A COMPARATIVE STUDY OF EFFICACY AND SAFETY OF TOPICAL MOMETASONE 0.1% WITH PLACENTAL EXTRACT VERSUS TOPICAL MOMETASONE 0.1% WITH TOPICAL TACROLIMUS 0.1% IN VITILIGO

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

in partial fulfillment of the

regulations for the award of the degree of

M.D. (PHARMACOLOGY)

BRANCH – VI

GOVT. STANLEY MEDICAL COLLEGE & HOSPITAL

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI, INDIA

MAY 2019

CERTIFICATE

This is to certify that this dissertation entitled "**A Comparative study of Efficacy and Safety of Topical mometasone furoate 0.1% with Topical placental extract Versus Topical mometasone furoate 0.1% with Topical tacrolimus 0.1% in vitiligo**" by the candidate Dr. A.PREETHI , for M.D. (Pharmacology) is a bonafide record of the research work done by her under the guidance of Dr.M.KULANDAIAMMAL, D.G.O, M.D., Professor and Head, Department of Pharmacology, Government Stanley Medical College, during the period of study (2016- 2019), in the Department of Pharmacology, Government Stanley Medical College,Chennai-01.

I also certify that this dissertation is the result of the independent work on the part of the candidate.

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DECLARATION

I hereby declare that this dissertation entitled in **"A Comparative study of Efficacy and Safety of Topical mometasone furoate 0.1% with Topical placental extract Versus Topical mometasone furoate 0.1% with Topical tacrolimus 0.1% in vitiligo "** was written by me in the Department of Pharmacology, Government Stanley Medical College and Hospital, Chennai under the guidance and supervision of **Dr.M.Kulandaiammal,D.G.O, M.D.,** Professor and Head, Department of Pharmacology, Government Stanley Medical College, Chennai – 600 001.

This dissertation is submitted to The Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the university regulations for the award of Degree of M.D., Pharmacology(Branch -VI) Examination to be held in May 2019.

Date:

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This is to certify that this dissertation work titled **"A Comparative study of Efficacy and Safety of Topical mometasone furoate 0.1% with Topical placental extract Versus Topical mometasone furoate 0.1% with Topical tacrolimus 0.1% in vitiligo "** of the candidate **Dr.A.Preethi** with registration number **201616051** for the award of **M.D. Pharmacology** in the branch of **VI**. I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows **3** percentage of plagiarism in the dissertation.

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Title of the Work : A Comparative study of efficacy and safety of topical mometasone furoate with placental extract versus topical mometasone furoate with topical tacrolimus in vitiligo.

Principal Investigator : Dr. A Preethi

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The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 24.02.2017 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

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CONTENTS

ABBREVIATIONS

GV - Generalised vitiligo

NSV - Non segmental vitiligo

SV - Segmental vitiligo

PUVA - Psoralen and ultraviolet A

BSA - Body surface area

DOPA - Dihydrophenyl alanine

HPE - Histopathological examination

MHC - Major histocompatibility complex

CTLA - Cytotoxic T lymphocytic antigen

FOXP1 -Forkhead box p1

AIS - Autoimmune susceptibility

INF - Interferon

TLR -TOLL like receptors

UVR - Ultraviolet Radiation

NMDA -N Methyl-D-Aspartate

ORS - Outer root sheath

MEL - Monochromatic excimer light

FDA - Food and drug administration

NF-ATC -Nuclear factor activated T cells

TNF α - Tumor necrosis factor alpha

VASI - Vitiligo area scoring index

BUN - Blood urea nitrogen

SV - Stable vitiligo

GM-CSF- Granulocyte macrophage colony stimulating factor

COMT - Catechol-O-methyltransferase.

INTRODUCTION

INTRODUCTION

Vitiligo[1] is an idiopathic , acquired , depigmentation disorder of the skin and hair . Vitiligo is one of the commonest skin disorder affecting about 1 to 2 % of world population . The incidence of the vitiligo[2] has been recorded highest in Indians and then followed by Mexican and japanese . Vitiligo occurs in all race , affects both sexes and presents in childhood and adults[3]. Vitiligo causes cosmetic disfigurement which leads to profound psychological distress and severe depression.

Typical vitiligo lesions are characterised by milky white , non scaly macules with clearly defined margins . It mainly involves hands, wrist, axilla, periorbital, perioral and anogenital skin.

It is a progressive depigmenting disorder[4] in which some or all of the melanocytes in the interfollicular epidermis and occasionally melanocytes in hair follicles are selectively destroyed. The main pathogenesis in vitiligo is due to autoimmune destruction of melanocytes.

Theories concerning vitiligo have concentrated on four different mechanisms which include autoimmune, oxidant- antioxidant, autocytotoxic, and neural. Vitiligo is also associated with other autoimmune disorders[5] such as pernicious anemia , Addison disease , Diabetes mellitus and auto immune thyroiditis.

The main treatment modality for Vitiligo includes dermatological agents like steroids, vitamin D analogues , PUVA therapy, helio therapy , lasers and skin grafting. Depending upon the body surface area of vitiligo, the treatment of choice varies. For stable vitiligo , where the involvement of depigmented macules is less than 20 % of BSA, the main modality of treatment is topical steroids with adjunctive treatment. Topical mometasone as a monotherapy is found to be effective in children in vitiligo. Even though topical mometasone remains the first line treatment in vitiligo involving less than 20% of BSA , it cannot be used for a longer duration due to its adverse effects. Topical placental extract , a newer drug used as an adjuvant along with steroids in stable vitiligo.

Topical tacrolimus , an immunomodulator , calcineurin inhibitor added to the newer armemantarium in treatment of vitiligo. Fewer studies have already proven that it is effective and response is surprisingly very good in stable vitiligo in children.

In this study , Efficacy and Safety of topical tacrolimus in combination with topical mometasone was well studied and compared with standard treatment, topical mometasone with topical placental extract.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

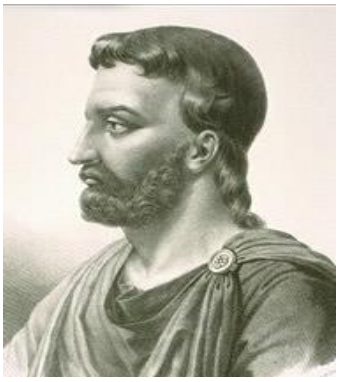
Vitiligo is an acquired depigmentation disorder of the skin due to progressive and selective destruction of functional melanocytes .

HISTORICAL ASPECTS:

- Celsus[6] coined the term vitiligo in his Latin medical classic De Medicina during the second century BCE. The name *"vitiligo"* is derived from the Latin word *"vitium"*, which means "defect or blemish".

- An Ancient text book of Ayurvedic Medicine , "The Charaka Samhita" recorded a diagnosis called '*svitra'* meaning ' whiteness' for vitiligo

- A Collection of Japanese Shinto prayers[7] *'Amarakosa'* dated from 1200 BC , given the accurate descriptions for vitiligo.



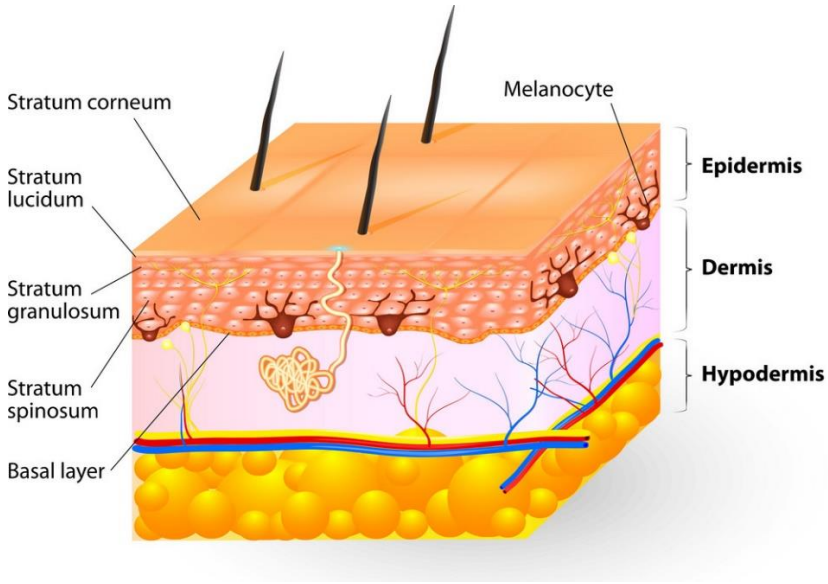
celsus

ANATOMY OF SKIN AND MELANOCYTES

The Integumentary system[8] is composed of skin and its structure. The Skin is the largest organ of our body accounts for 15% of total body weight . skin is comprised of three layers: Epidermis , Dermis , Subcutaneous tissue .

Epidermis is the outermost layer of skin[9] and give rise to various derivative structures like pilosebaceous apparatuses, nails and sweat glands. The Dermis is the middle layer , fundamentaly made up of collagen which is the fibrillar structural protein .The Inner most layer is subcutaneous tissue or panniculus , consist of fat cells known as lipocytes.

Figure 1: ***Skin and skin appendages***



The epidermis[10] is a stratified squamous epithelial layer primarily composed of two types of cells : keratinocytes and dendritic cells . Epidermis also harbors few other cell populations such as melanocytes, langerhan cells and merkel cells.

Keratinocytes[11] constitutes about 80% of the cells in epidermis . It is ectodermal in origin and mainly present in the basal layer of epidermis. Keratinocytes undergoes a differentiation process in which cells migrate from the basal layer of epidermis to the superficial layer of the skin results in *keratinization* **.** It also synthesizes keratin which has a protective role.

The Epidermis is commonly subdivided in to four different layers according to the morphology of keratinocyte and position of its differentiation in to horny cells .

Four layers of epidermis[10]

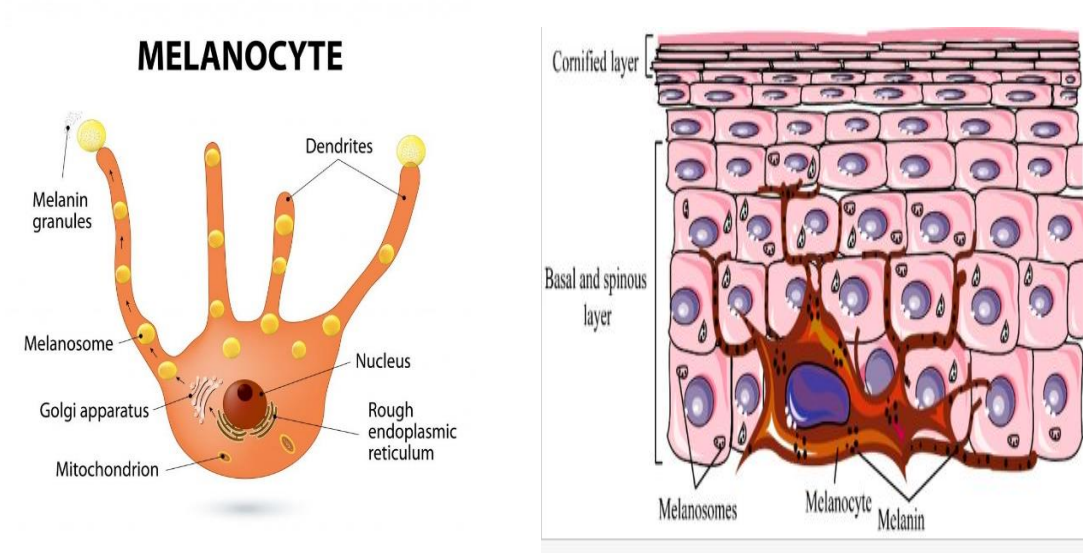
1. Stratum corneum (Cornified / horny cell layer)
2. Stratum granulosum (Granular cell layer)
3. Stratum spinosum (Squamous cell layer)
4. Stratum germinatum (Basal cell layer)

MELANOCYTES:

Melanocytes[12] are neural crest derived dendritic cells responsible for the production of melanin pigment . It is mainly present in skin and hairfollicles . Melanocytes are also found in other tissues like cochlea(inner ear), uvea of eye, bones, heart and brain of human.

In the skin[13-15], it is confined to the basal layer of epidermis and hair follicles, the dendrites of melanocytes will branch in to the superficial layers of epidermis .

Figure 2: ***Structure of melanocyte***

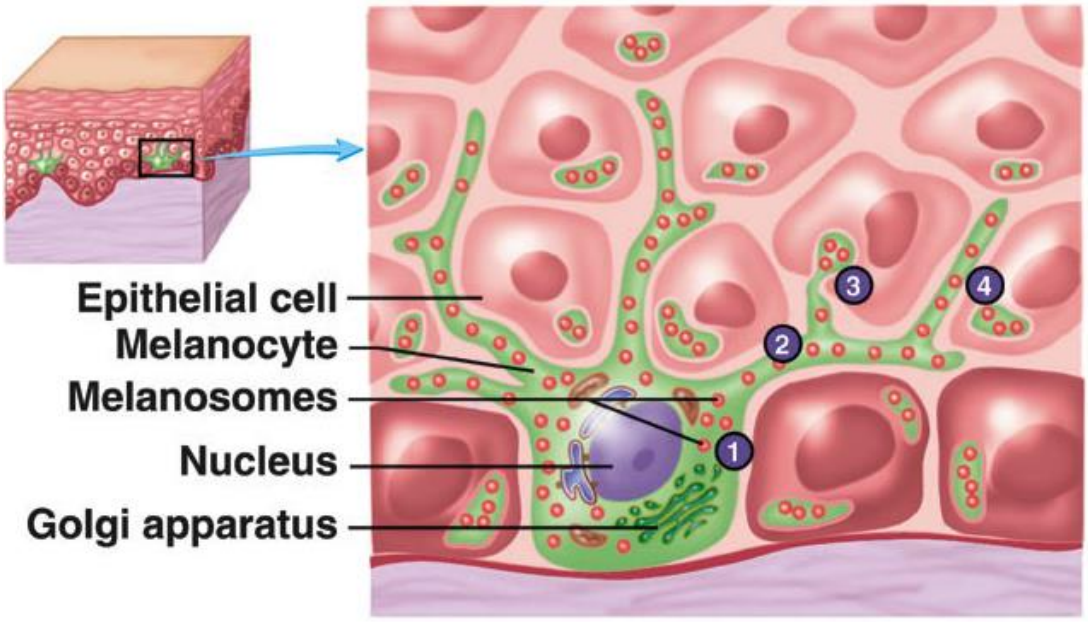


Due to various stimuli such as intrinsic and extrinsic factors, the precursors of melanocytes gets differentiated and give rise to melanocytes. Melanocytes[14] then

produces melanin pigment (melanogenesis) through a series of hormone stimulated, receptor mediated and enzyme catalysed reactions.

Melanin[16] is endogenously synthesized and stored inside the membrane bound organelles known as '*melanosomes'* present within the cytoplasm of melanocytes.

Figure 3: ***Epidermomelanin unit and distribution of melanosomes***



EPIDERMAL MELANIN UNIT[17]

In a normal human skin, almost every tenth cell in the basal layer of epidermis is a melanocytes which is surrounded by kerationcytes. The epidermal melanin unit

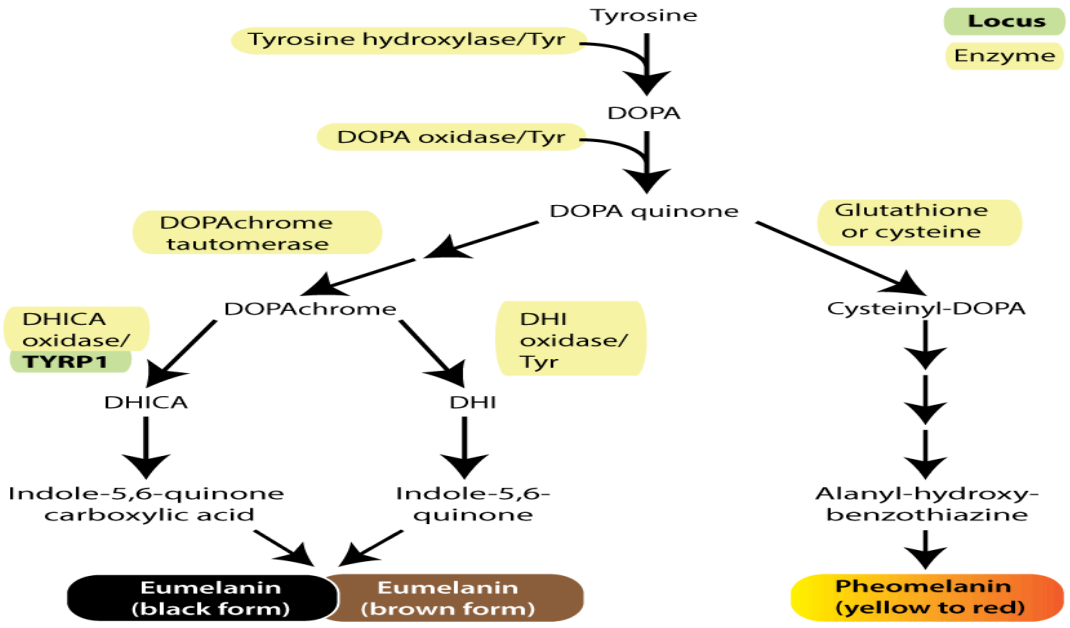
refers to association of one melanocytes with 30 to 36 keratinocytes to which it transfers melanin containing melanosomes.

Melanosomes from the cytoplasm of melanocytes are moved to the end of dendritic end and then melanin pigment are transferred to the surrounding keratinocytes.

BIOSYNTHESIS OF MELANIN[18]:

Melanin are pigment molecules which are synthesised by genetically predetermined melanocytes. Melanin pigment formation is a complex biochemical process starts from the conversion of aminoacid precursor tyrosine to its metabolite DOPA

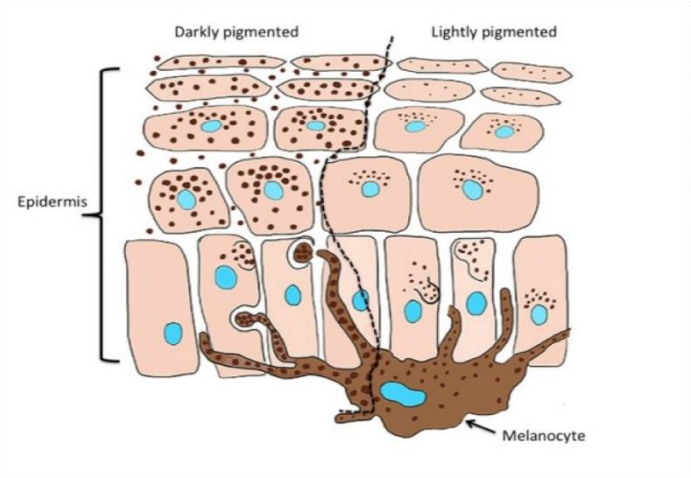
Figure 4 : *Biosynthesis of melanin*



Functions of melanin pigment[19]:

1. The molecular structure of melanin helps in absorbing UV and visible light hence it serves as a protector against ultraviolet radiation from sunlight.
2. Melanins are powerful chelators and acts as a free radical sinks.
3. Due to its light absorption property, it plays a vital role in photoreceptor shielding, photoprotection , thermoregulation and display coloring.
4. Melanin is responsible for the complexion of skin . In white skin, membrane bound melanosome complexes containing two or three melanosomes are aggregated, whereas in dark skin individuals, melanosomes complexes tend to be removed more rapidly in keratinocytes of individuals with dark skin.

Figure 5: ***Melanin distribution and pigmentation***



Darkly pigmented skin[20] is mainly due to

- The Greater production of melanosomes in melanocytes.
- Larger size of melanosomes.
- The Higher degree of melanization in each melanosome.
- Slower rate of melanosome degradation in comparison to fair skin .
- The Greater amount of dispersion of melanosomes in keratinocytes.

CLASSIFICATION OF VITILIGO

Vitiligo is broadly classified to two major forms

1. Non segmental vitiligo
2. Segmental vitiligo

NON SEGMENTAL VITILIGO[21-23]

Non segmental vitiligo is the commonest form of vitiligo . It is characterised by symmetrical and white patches. Usually there is a bilateral distribution scattered uniformly all over the body/ acrofacial pattern. It may slowly progress to generalised/universal form.

Few studies suggest that two phenotypes of non segmental vitiligo have been identified.

1. Early onset NSV less than 12 years of age associated with halo naevus
2. Late onset NSV and often associated with an acrofacial pattern

Subgroups of Non segmental vitiligo:

1. **Acrofacial vitiligo:**

   Clinical form of NSV involving digits and facial region which is usually difficult to treat . It occurs predominantly in the initial stage of characterised by macules in distal digits , periorificial facial region and sometimes in the anogenital areas.

2. **Mucosal vitiligo:**

   It is a form of NSV which will present as the extension of acrofacial pattern or it may occur in pure mucosal forms.

3. **Generalised vitiligo :**

   Most commonest form of NSV involves depigmentation of skin all over the body like in the face, neck , scalp , trunk and limbs.

4. **Mixed vitiligo[24]:**

   The coexistence of non-segmental and segmental vitiligo in the same patient is called mixed vitiligo

5. **Vitiligo minor/ hypochromic vitiligo**:

   It is a rare clinical variant , subgroup of NSV. It is generally limited to the dark skinned individuals . The term ‘minor’ refers to the partial defect in pigmentation with pale skin color compared to healthy skin. conventional vitiligo macules in the HPE supports the relation with true vitiligo.

SEGMENTAL VITILIGO

Segmental vitiligo[25] is a less common form vitiligo accounting for 5–16% of overall vitiligo cases. It is characterised by patchy[26] and progressive loss of pigmentation from skin , overlying hair and mucosa.

Lesions[27] are typically unilateral , distributed in band shaped pattern / segmentally.

Further classified in to three types[28]:

1. Unisegmental
2. Bisegmental
3. Pleuri segmental

CLINICAL VARIANTS OF VITILIGO:

1. Halo naevi-associated leukoderma:

This is a form of hypomelanosis similar to melanoma-associated leukoderma, where discrete areas of depigmentation develop in skin away from the halo naevi . This disorder differs from classical vitiligo in that the depigmented macules not as clearly demarcated from normal skin as in vitiligo and are often more limited that will not progress. The phenomenon results from a temporary autoimmune process which is directly linked to the halo phenomenon

2. **Inherited or genetically induced hypomelanosis**

It is usually present at birth.

- Pigmentary mosaicism (hypomelanosis of Ito).
- Waardenburg syndrome.
- Piebaldism.
- Tuberous sclerosis.

3. Progressive macular hypomelanosis.

4. Secondary hypomelanosis.

• Post-inflammatory hypomelanosis.

• Post-traumatic hypomelanosis, post-infectious hypomelanosis.

RARE CLINICAL PHENOTYPES OF VITILIGO[29]:

1. Vitiligo minor(hypochromic vitiligo)

2. Follicular vitiligo

3. Red vitiligo: The depigmented macules are surrounded by raised erythematous border

4. Blue vitiligo :

The depigmented skin shows bluish gray appearance . On HPE, there is alternative absence of epidermal melanocytes followed by presence of dermal melanocytes corresponding to blue-gray appearance of skin.

5. Trichrome vitiligo : It is characterised by tricolor appearance of depigmented macules.

6. Quadrichrome vitiligo : It appears as 4 different shades of depigmented skin.

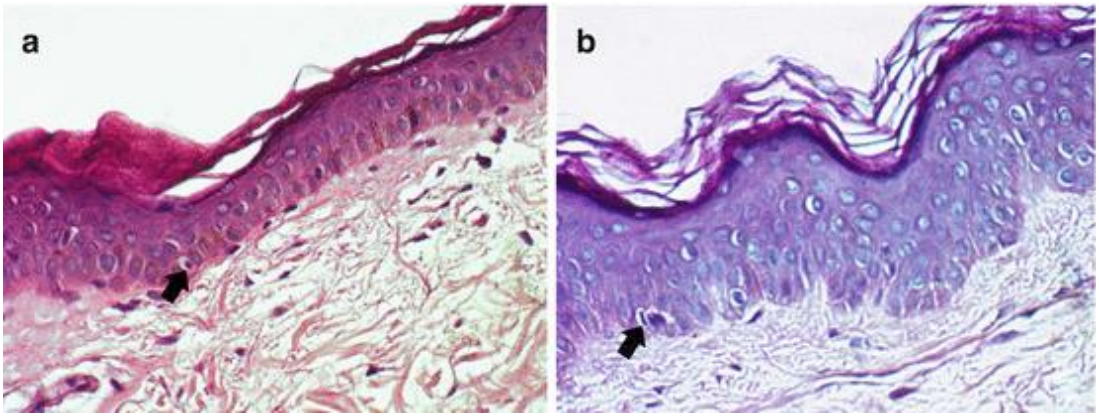
7. Pentachrome vitiligo : It refers to 5 different shades of colored depigmentation in the skin

8. Confetti vitiligo : These are tiny punctuate type of depigmented macules on a hyperpigmented macule.

HISTOPATHOLOGY[30]:

- **Histochemical Analysis** shows that there is a lack of dopa positive melanocytes in the basal layer of epidermis .
- Studies related to **Immunohistochemical analysis** with large panel of antibodies implicated that only small amount of melanocytes are present in lesional skin.
- Studies on **electron microscopy** confirm the absence of melanocytes in the depigmented skin lesions. It also reveals that there is abnormalities of keratinocytes and degenerating melanocytes are present in the epidermis around the margins of vitiligo.
- Some studies also reveals that, biopsy taken from the active stage of inflammatory vitiligo shows infiltration of lymphocytes, histiocytes and raised erythematous border in the margins of lesions.

Figure 6 : ***HPE of stable vitiligo***



ETIOPATHOGENESIS

Vitiligo is a complex , multifactorial, polygenic disorder involving multiple pathogenic mechanisms

- Genetic
- Non genetic factors

GENETICS IN VITILIGO[31-35]

Many epidermological surveys done in large scale have shown that Vitiligo occur sporadically in most of the cases . Various survey shows that first degree trelatives have been affected for about 15-20%, this implies that there is a definite component is involved in vitiligo.

Eventhough , Familial clustering occurs in vitiligo , only 23% of monozygotic twins shown concordance in inheritance of vitiligo. This concludes that both genetic and nongenetic factors like environmental factors also plays a role in pathogenesis of vitiligo.

Usually genetic inheritance in a family involves a non mendelian pattern suggestive of polygenic, multifactorial factors in etiopathogenesis of vitiligo.

Genetics in Generalised vitiligo

Several studies have been done to test the genetic association of generalised vitiligo

Multiple candidate genes in GV includes

- Major histocompatibility complex (MHC)
- Genes encoding enzymes like catalase, angiotensin convertin enzyme, COMT, protein tyrosine phosphatase
- Cytotoxic T lymphocytes antigen CTLA 4, Human leukocyte antigen HLA
- NACHT, leucine rich repeat protein NALP1
- X box binding protein XBP1, interleukin IL2 receptor A and forkhead box p1 (FOX P1)

Genetics in Segmental vitiligo[33]

Segmental vitiligo have been associated with genetical mechanism distinct from generalised vitiligo. It is usually sporadic in nature results from somatic mutation of genes that are essential for melanoblast , melanocyte differentiation/ survival. This hypothesis is although controversial .

Gene expression profiling was done in patients with segmental vitiligo , non segmental vitiligo and normal healthy individual using highthroughput whole genome expression microarrays.

In this analysis , two different genetic mechanism is involved for segmental vitiligo and nonsegmental vitiligo

In **Segmental vitiligo**, genes are expressed differently from healthy individual in which the genes are involved in the normal adaptive immune response , focal adhesion, cytokine-cytokine receptor interation and sphingolipid metabolites.

In **Nonsegmental vitiligo**[34] , altered gene expression is involved in controlling autophagy, melanocyte biology , tyrosine metabolites and apoptosis.

Some studies involving genome wide linkage analysis shows that autoimmune susceptility (AIS) loci was associated with vitiligo

- AIS 1- chromosome 1p 31.3 – p 32.2
- AIS 2- chromosome 7
- AIS 3- chromosome 8

Sahmotova et al in his study found that mi RNA mi R155 were over expressed leading to altered INF- regulated genesis melanocytes , keratinocytes and other melanocyte associated genes.

In the study by traks et al reviewed the role of TLRS and found that single nucleotide polymorphism in TLR 7 is associated with vitiligo made them a role in future targeted therapies.

NON GENETIC FACTORS[36-38]:

Vitamin D deficiency

Vitamin D3 is a fat soluble vitamin synthesized in the skin from 7 dehydrocholesterol under the influence of ultraviolet light . Vitamin D3 bind to Vitamin D receptor present in the cells that regulates calcium and bone metabolism , controls cell proliferation of keratinocytes,melanocytes and fibroblast and exert immunoregulation.

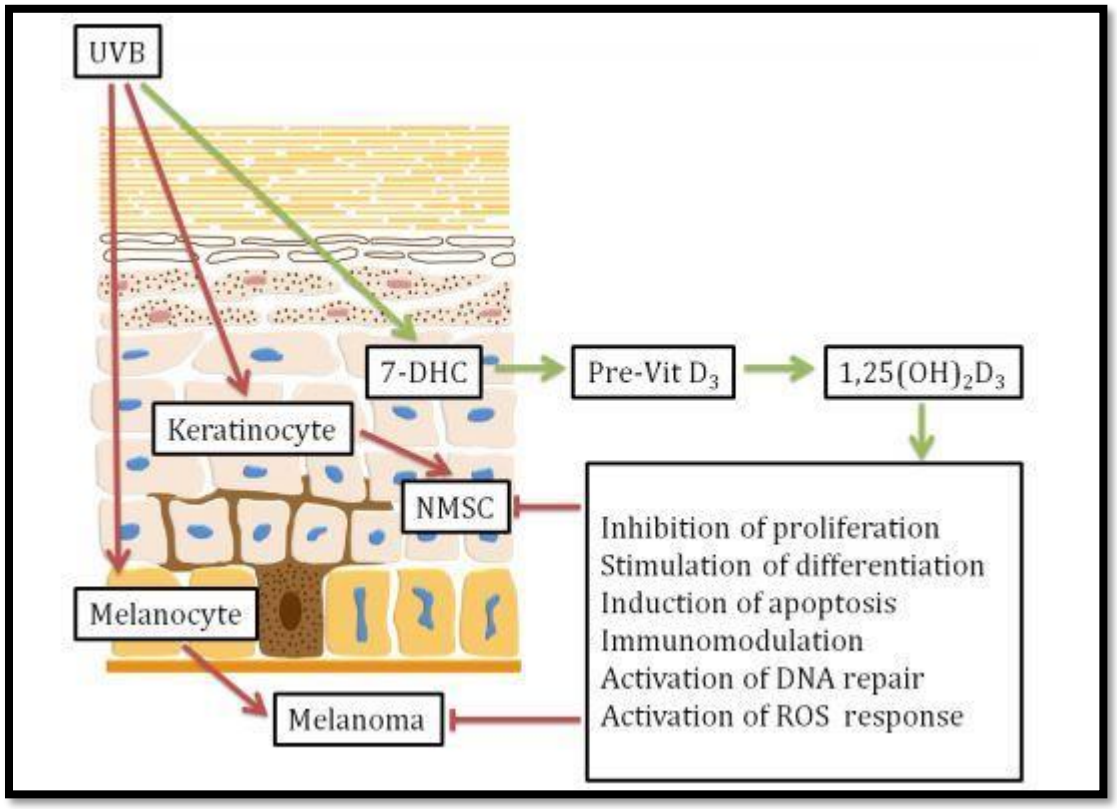
Some of the invitro studies have proven that vitamin D3 contributes to repigmentation of vitiligo macule by increasing the melanogenesis and tyrosine content of cultured human melanocytes thereby protecting the melanocytes from UV B induced apoptosis.

In a systematic review and melanocytes by upala et al shows that when comparing to healthy individuals, there is significantly lower concentration of serum 25 OH Vit D was present in patients with vitiligo.

Main reason for decrease in Vitamin D in vitiligo patients

- Autoimmune diseases lower vitamin D3 level.
- Decreased exposure to sunlight.

Figure 7: Role of vitamin D in vitiligo



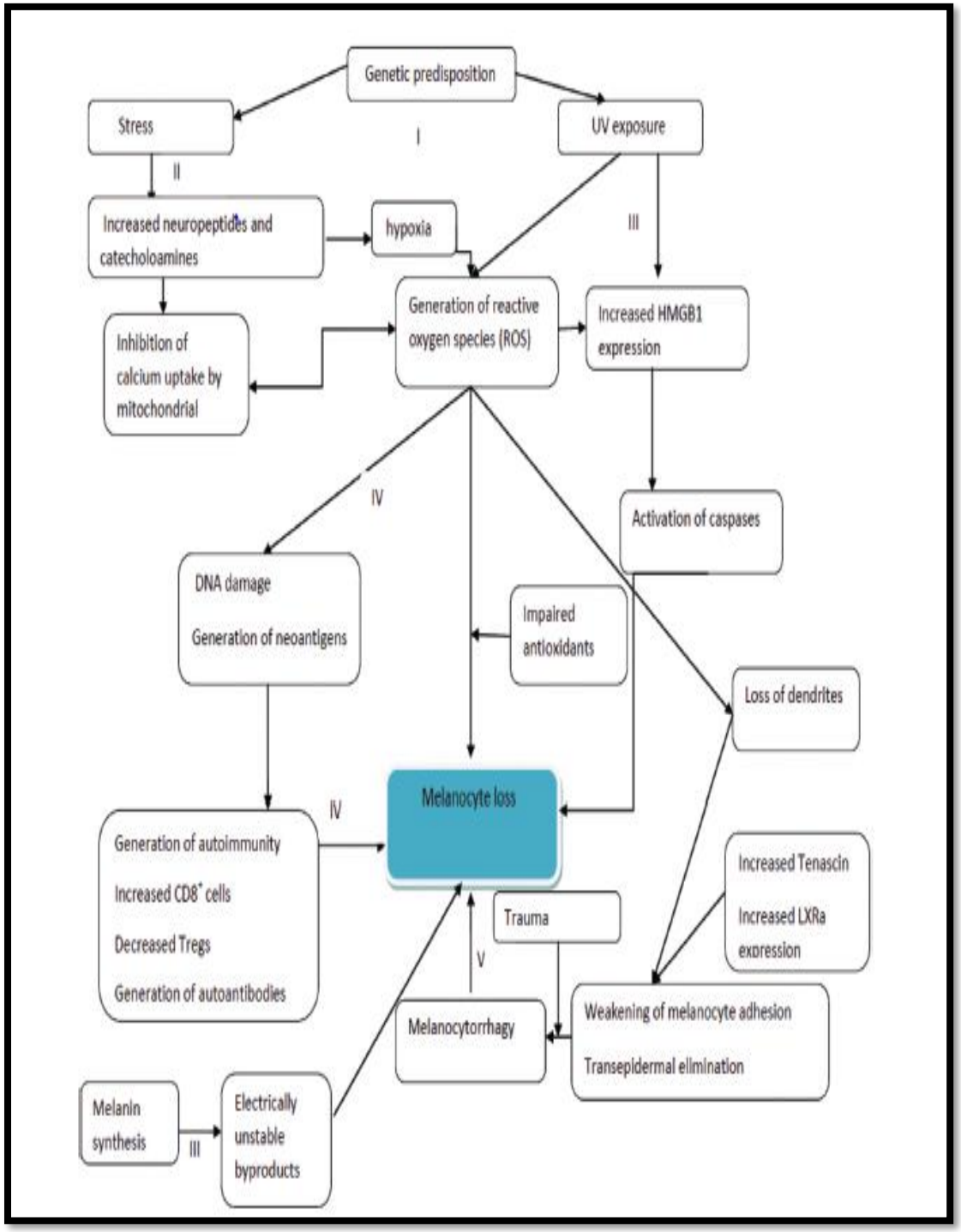
Other mechanisms proposed for vitiligo:

- Autoimmune hypothesis
- Oxidative stress
- Autocytotoxicity
- Melanocytorrhagy
- Deficiency of survival signals
- Neurohumoral hypothesis
- Hyperhomocystinemia

Autoimmune disorders associated with vitiligo[39-40]

- Thyroid disease
- Addison's disease
- Pernicious anemia
- Diabetes
- Myasthenia gravis
- Halo naevus
- Malignant melanoma

Figure 8: PATHOGENESIS OF VITILIGO



DIFFERENTIAL DIAGNOSIS:

A Skin biopsy is rarely required to confirm the diagnosis of vitiligo due to similar type of morphological features in other hypomelanotic skin diseases .

DIFFERENTIAL DIAGNOSIS OF GENERALISED VITILIGO[41]

1. Infectious disorders

- Tinea versicolor
- Secondary syphilis
- Tuberculoid/borderline leprosy

2. Idiopathic disorders:

- Post inflammatory pigmentary loss.
- Idiopathic guttate hypomelanosis

3. Inherited Hypomelanosis:

- Piebaldism
- Tuberous sclerosis
- Waardenburg's syndrome

4. Postinflammatory hypopigmentation

- Scleroderma
- Discoid lupus erythematosus

5. Paramalignant hypomelanosis

- Mycosis fungoides
- Cutaneous melanoma

6. Toxin induced depigmentation

7. Drug induced depigmentation

- Imatinib
- Chloroquine
- Fluphenazine
- Physostigmine
- Topical imiquimod

DIFFERENTIAL DIAGNOSIS FOR LOCALIZED VITILIGO

- Nevus depigmentosus
- Nevus anemicus

DIAGNOSIS

The diagnosis of vitiligo is established primarily based on clinical findings, which may include history, nature of disease ,distribution and extent of lesions .

LABORATORY FINDINGS

Since there is association between vitiligo and other autoimmune diseases well established, numerous screening laboratory tests are helpful, including T4 and thyroid-stimulating hormone levels, antinuclear antibodies and complete haemogram. consider testing for serum antithyroglobulin and antithyroid peroxidase antibodies, especially when patients having signs and symptoms suggestive of autoimmune thyroid disease.

CLINICAL COURSE AND PROGNOSIS

The Clinical course of Generalised Vitiligo is always unpredictable , but it is typically gradually progressive and quiet difficult to control with therapy. Sometimes lesions spread over time, whereas in other scenarios disease activity stops, persisting in stable status for a long period. The prognosis also takes a different path in generalised vitiligo.

The indicators of poor prognosis:

- Involvement of mucosa and acral region.
- Long duration of the disease.
- Occurrence of Koebner's phenomenon.
- Occurrence of leukotrichia.

MANAGEMENT OF VITILIGO

THE FUNDAMENTALS OF VITILIGO THERAPY:

MELANOCYTE REPOPULATION

The Main principle of vitiligo therapy is facilitate the repopulation of depigmented patches of the interfollicular epidermis with active differentiation of melanocytes that are able to migrate, survive to repopulate the depigmented skin and involves melanin biosynthesis. Repigmentation may occur spontaneously and may also be vitiligo therapy induced.

Spontaneous repigmentation is almost unpredictable, clinically insignificant and tends to cause cosmetic disfigurement. It occurs in less than 50% of patients, most commonly in younger individuals and in sun-exposed areas, where natural sunlight act as an inducing agent. Clinically , the most commonly

encountered pattern of repigmentation is perifollicular , even though other patterns, such as marginal, diffuse, or combined also may occur.

The principal source of melanocytes involved in repigmentation of vitiligo skin is most likely due to melanocyte precursors derived from the outer root sheath (ORS) or bulge area of the hair follicle.

A Secondary potential reservoir will be located near lesional borders of depigmented skin. The middle and lower parts of the ORS are crowded by DOPA-negative, amelanotic melanocyte which can be recruited from the ORS of the hair follicle in response to ultraviolet (UV)B, corticosteroids and stimuli related to treatment of vitiligo.

As a result, the number of melanocytes in the ORS of hair follicles increases tremendously and become active, suggesting that melanocyte precursors proliferate and some of them undergo maturation. Activated ORS melanocytes possess all of the structural and enzymatic proteins required for melanogenesis, proliferation and maturation as they migrate up the nearby epidermis, where they spread centrifugally and form perifollicular pigment groups. Then they become larger cells, with intense DOPA oxidase activity.

Vitiligo repigmentation is evaluated in terms of the proportion of treated subjects in whom a specified degree of repigmentation more than 50% or more than 75% may be considered as good response.

Wood's lamp (UVA) examination is helpful to monitor response to therapy. In the absence of epidermal melanin unit, otherwise it absorbs most of the UVA light, where more photons will reach the dermis, where they are absorbed by collagen that then fluoresces and emits bright visible light.

In contrast, visible wavelengths are less well absorbed by melanin in the normally pigmented epidermis than UVA wavelengths and do not produce fluorescence in the dermis. Therefore, under Wood's light the vitiligo area appears brighter and the normal skin appears usually darker than when illuminated with ambient room light .

THERAPEUTIC APPROACHES IN VITILIGO

Multimodal treatment strategies have been proposed to inhibit the immune response in vitiligo, reduces the melanocyte destruction and enhance the epidermal repopulation by melanocytes, both by stimulating recovery of damaged melanocytes and also by reactivating residual melanocytes or stimulating melanocyte insitu migration from neighboring skin or hair follicles. Inspite of all

this, it is not clearly understood that the extent of each treatment suppressing the autoimmune process and stimulating melanocyte repopulation of the epidermis to provide maximum efficacy in treatment.

ULTRAVIOLET RADIATION THERAPY[42]

UV radiation therapy includes phototherapy with narrowband UVB /broadband UVB and photochemotherapy. UV therapy is found to act as a skin immunomodulator, which regulates the activity of inflammatory cytokines, modulating the activity of regulatory T cells and polarize the immune response toward the Th2 profile, therefore reduces or stabilizes the depigmentation process in vitiligo. UV radiation coordinates many of the pathways through melanogenic cytokines stimulate melanogenesis. UV also induce the release of epidermal factors which stimulate melanocyte proliferation and migration, Even though this speculation had not been well substantiated in repigmentation of vitiligo lesions.

ULTRAVIOLET B NARROWBAND[43-46]

Narrowband UV (NB-UVB) light, peak emission at 311 nm, is the most effective and safest current therapy for vitiligo, and thus it is first line mode of treatment of choice for patients with moderate to severe Generalised vitiligo. Few studies assessing psoralen and UVA (PUVA) against NB-UVB shows that NB-UVB produces higher repigmentation rates and better patient satisfaction. NB-UVB had

still fewer short-term adverse reactions such as painful erythema and also some long-term side effects such as epidermal thickening and photocarcinogenesis than PUVA.

Recent clinical studies have been reported high rates (≥75%) of repigmentation in at least 40% of patients whom were treated with narrow band UV- B. The most recently accepted NB-UVB protocol involves twice-weekly administration of a fixed starting dose of 0.21 J/cm2, slowly increasing the dose by 20% at each session till the minimal erythema dose has been reached. Roughly nine months of therapy will be required to achieve desired maximal repigmentation of skin . At least 3 months of treatment are required to conclude the condition in which the above treatment can be classified as nonresponsive. The most responsive sites for this type of therapy are face, trunk, and limbs and the least responsive sites are mainly hands and feet.

PHOTOCHEMOTHERAPY (PUVA)

Till now ,PUVA was accepted as the mainstay of therapy for patients diagnosed with widespread vitiligo. PUVA includes of a combination of topical or oral 8-methoxypsoralen with UVA (320–400 nm) irradiation. The most common psoralen of choice, methoxsalen, is given in an oral dose of 0.4-mg/kg body weight, usually 1–2 hours prior to UVA exposure.

For instance it is a topical PUVA therapy, methoxsalen 0.1% should be applied to areas of vitiligo 30–60 minutes before exposing to UV radiation. Topical PUVA is prefered in patients whom vitiligo involves less than 20% of the body surface area and painful burns (phototoxicity reactions) is expected with other treatments.

Oral psoralens can be used for patients with more extensive involvement or in patients who do not respond to topical PUVA. After oral treatment, patients must wear UVA-blocking glasses, and it is also recommended they use broad-spectrum sunscreens and wear protective clothing. Patients with darker complexions tend to respond best to PUVA, possibly because they tolerate higher PUVA exposures. PUVA is strictly not recommended for usage in children under the age of 12 years leading to the long-term delayed risks of cataract formation and skin cancer.

TOPICAL VITAMIN D DERIVATIVES

Vitamin D analogues are calcipotriol ointment (0.005%) and tacalcitol ointment (20 μg/g) which will restore repigmentation in vitiligo by inducing skin immunosuppression, which also suppresses the local autoimmune process and act via direct activation of melanocytic precursors and melanogenic pathways.

Some recent studies report more effective repigmentation can be achieved in vitiligo when vitamin D analogs are used as adjunctive therapy because of more complex activation of the repopulation process, targeting both melanocyte growth with corticosteroids and differentiation by vitamin D analog . Vitamin D derivatives are indicated for use in localized vitiligo and the benefits includes no skin atrophy and easy for application. Vitamin D analogs role in vitiligo treatment remains controversial.

LASER THERAPY [47-48]

UV B narrowband excimer laser (XeCl) and monochromatic excimer light (MEL) are recently used in the treatment of localized vitiligo. These laser therapy are almost similar to classical NB-UVB treatments but have fewer side effects than later.

The XeCl have laser-coherent emission of monochromatic rays, where the MEL device can generate and deliver 308-nm UVB light selectively. only one lesion can be treated at a time. There are no risk of cancer and associated with only fewer side effects.

NONCULTURED EPIDERMAL SUSPENSIONS

This technique is done by grafting noncultured suspensions containing both keratinocytes and melanocytes suspensions are obtained by 0.25% trypsin digestion of a thin piece of donor skin and are injected into blisters raised by liquid nitrogen freezing or seeded on recipient sites denuded by superficial dermabrasion. An advantage of this method is lack of scarring if recipient and donor sites are carefully manipulated.

SURGICAL TREATMENT

Autologous skin grafts[49] are the ultimate treatment option in patients with stable vitiligo who are refractory or partially responsive to other medical treatment. This treatment option is confined to depigmentation involving less than 3% of body surface area. The most common side effects are infection, cobblestoning, postinflammatory hyperpigmentation and scarring. UV-light therapy and surgical methods improves repigmentation and fasten the recovery in vitiligo .

MINIGRAFTING

Minigrafting technique is the most commonly used surgical method for vitiligo treatment. Multiple perforations are made on recipient sites using 1.0–1.2-mm punches 3–4 mm apart from each other and then , minigrafts which are

harvested from the donor site using a similar punch, will be transferred to recipient sites using fine forceps or a hypodermic needle.

Repigmentation appears around each minigraft up to 2–5 mm due to coalescence of spreading pigment. The main advantage here is, it is a simple procedure and good results are obtained in refractory patients having lip type vitiligo. The main disadvantage is there is high chances of cobblestoning.

THIN DERMAL–EPIDERMAL GRAFTS[50]

Grafts are harvested at a depth of 0.1–0.3 mm and then it is placed directly under the recipient abraded depigmented skin next to each other where it is secured with surgical dressings under mild pressure . Then it is not disturbed for 1 week. Repigmentation occurs during the following weeks. Good response was reported on sites like dorsal hands and fingers.

EPIDERMAL GRAFTING [51-52]

Grafts are harvested at negative pressure from the donor sites like inner aspect of the thigh and the flexor aspect of the forearm using different custom-made suction devices. Recipient sites will be prepared by removing the epidermis slowly using liquid nitrogen freezing or superficial dermabrasion or laser ablation. This Epidermal grafts will be most appropriately used for lip vitiligo .

PSEUDOCATALASE[53-57]

Pseudocatalase has been an enzyme therapy which reconstitutes deficient activity of catalase in vitiligo epidermis, degrading excessive H2O2 and allows early repigmentation and recovering the enzyme activity in the skin. Pseudocatalase monotherapy or in combination with NB-UVB has shown significant efficacy in repigmentation and prevention of disease progression in some randomized uncontrolled trials, while in other studies showed no remarkable benefits .

MICROPIGMENTATION

Micropigmentation is the main stay of treatment for vitiligo lesions on mucous and mucocutaneous areas. It is a procedure of tattooing using multiple electrically driven needles, in which inert pigment granules are delivered into the dermis within collagen bundles and extracellularly at a depth of 1–2 mm. Combinations of various colours like white, yellow, black, red, and brown pigments are used.

CORTICOSTEROIDS[58]

TOPICAL CORTICOSTEROIDS

Topical corticosteroids remains the first-line therapy for localized vitiligo and are highly recommended for facial or small lesions and for use in children.

Advantages mainly includes ease of application, high compliance rate and low cost. Compared with PUVA, topical corticosteroids which promotes a perifollicular pattern of repigmentation. Topical corticosteroids results in more diffuse repigmentation, which occurs more quickly but it is less stable.

Light and electron microscopy of skin biopsies from control and steroid-treated areas showed marked repopulation by functional melanocytes in the repigmented vitiliginous skin. In the current situation , based on the results of a large meta-analysis of randomized controlled trials of 29 patient series, is that class 3 and 4 corticosteroids are the most effective for treatment for localized vitiligo.

Hence , localized lesions will be treated with a high-potency fluorinated corticosteroid (e.g., clobetasol propionate ointment, 0.05%) for 1–2 months. Then the treatment can be gradually tapered to a lower potency corticosteroid (e.g., hydrocortisone butyrate cream, 0.1%). Caution is warranted when using topical steroids over and around the eyelids, as their use can increase intraocular pressure and precipitate glaucoma. Vitiligo relapse after cessation of treatment and corticosteroid-induced side effects like skin atrophy, telangectasis, striae, and very rarely, contact dermatitis are the main limiting factors.

Commonly used Combination therapies

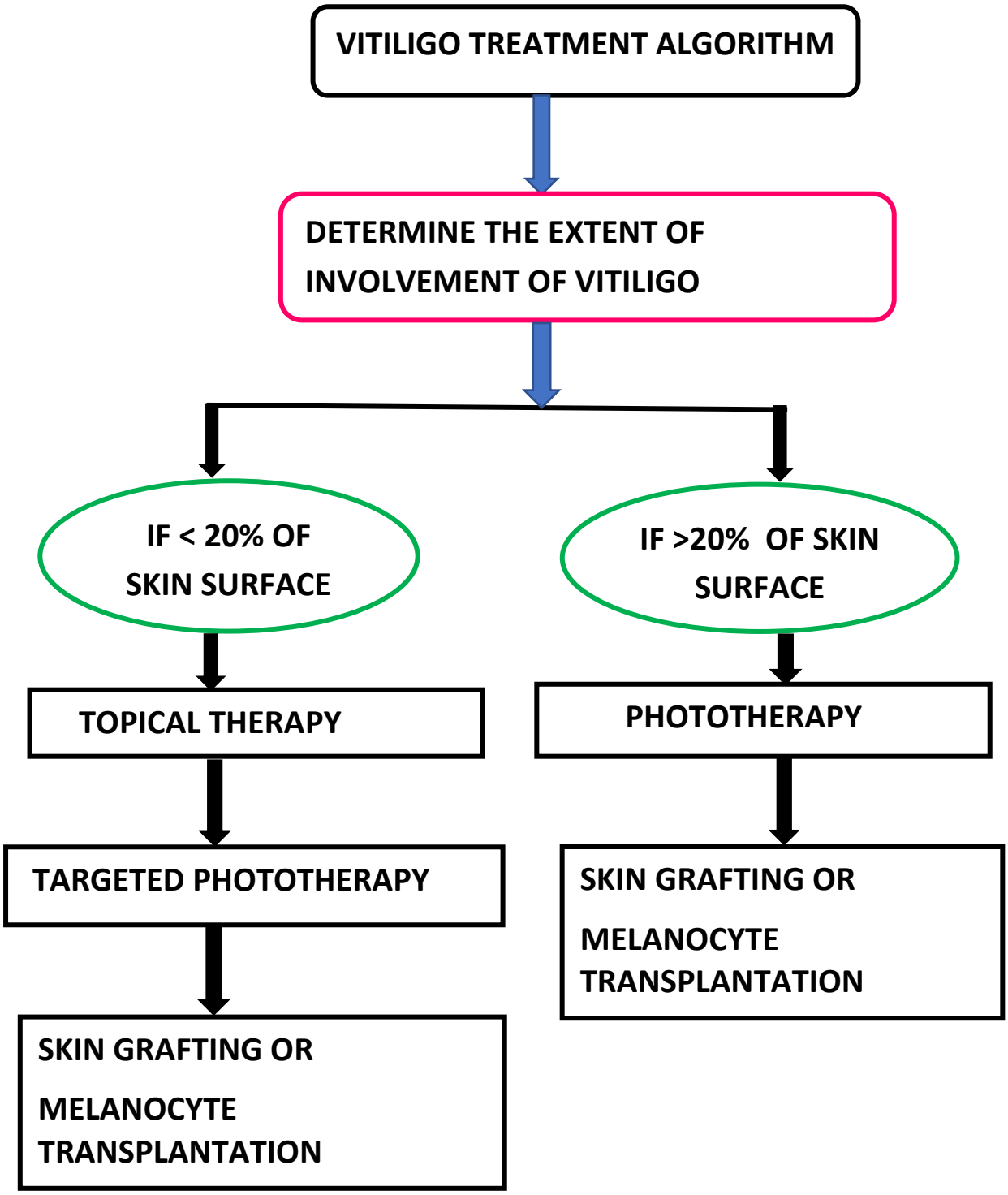
- Corticosteroids + UVB
- Corticosteroids + Calcineurin inhibitors
- Corticosteroids + Vitamin D analogs
- Corticosteroids + Placental extract

These combinations may be beneficial due to combination therapies,

- act synergistically on pigment restoration and acts on immune suppression.
- at lower individual doses , potentially minimizes overall side effects.

TREATMENTS FOR VITILIGO

	TOPICAL	**PHYSICAL**	**SYSTEMIC**	**SURGICAL**
FIRST LINE	1. Steroids 2. Calcineurin inhibitors	3. NB-UV 4. PUVA		
SECOND LINE	Calcipotriol	Topical PUVA	Steroids (pulse therapy)	Grafting Melanocyte transplant


VITILIGO TREATMENT ALGORITHM
DETERMINE THE EXTENT OF INVOLVEMENT OF VITILIGO
IF < 20% OF SKIN SURFACE
IF >20% OF SKIN SURFACE
TOPICAL THERAPY
PHOTOTHERAPY
TARGETED PHOTOTHERAPY
SKIN GRAFTING OR MELANOCYTE TRANSPLANTATION
SKIN GRAFTING OR MELANOCYTE TRANSPLANTATION

TOPICAL TACROLIMUS

Tacrolimus (FK 506)[59-61] is a 23 membered lactone macrolide antibiotic isolated from the fermentation broth of *Streptomyces tsukubaesis* . Tacrolimus is an immunosuppressive agent belongs to calcineurin inhibitor group which has been emerged as a valuable alternative to cyclosporine following solid organ transplantation.

The FDA approved uses are prevention of allograft rejection, prevention of acute rejection in liver transplantation, other organ transplants like lung, kidney, pancreas, heart.

Figure 9: *Chemical Structure Of Tacrolimus*

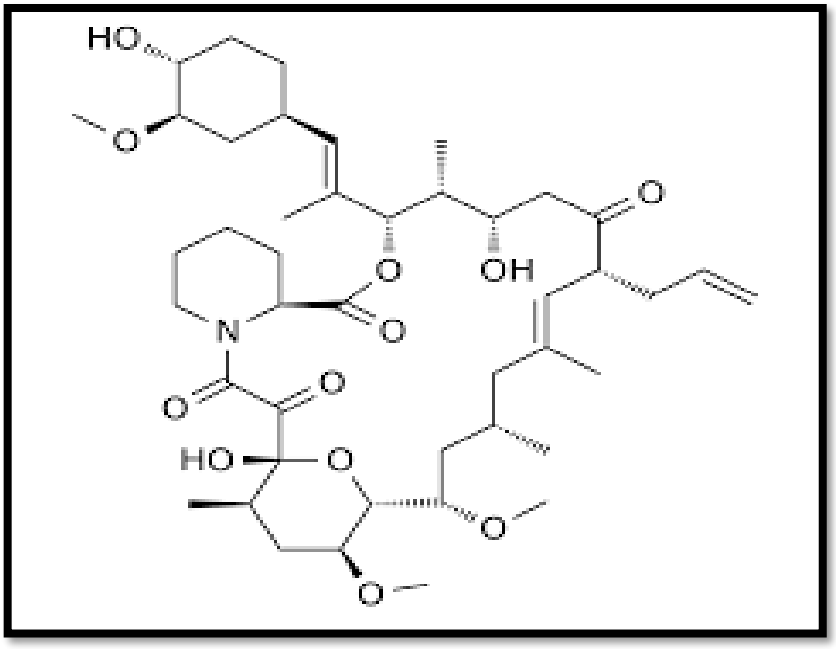
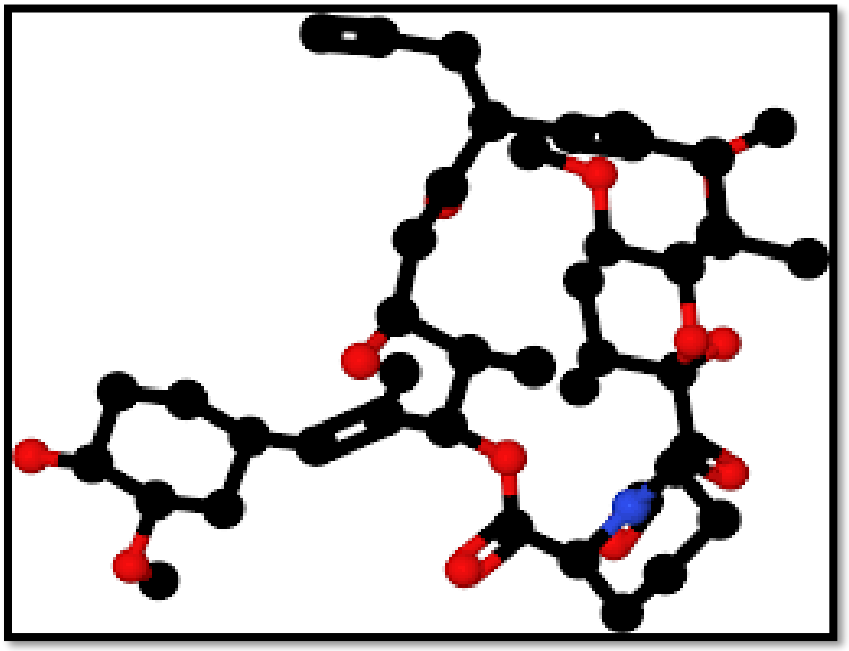


Figure 10: *Ball And Stick Structure Of Tacrolimus*

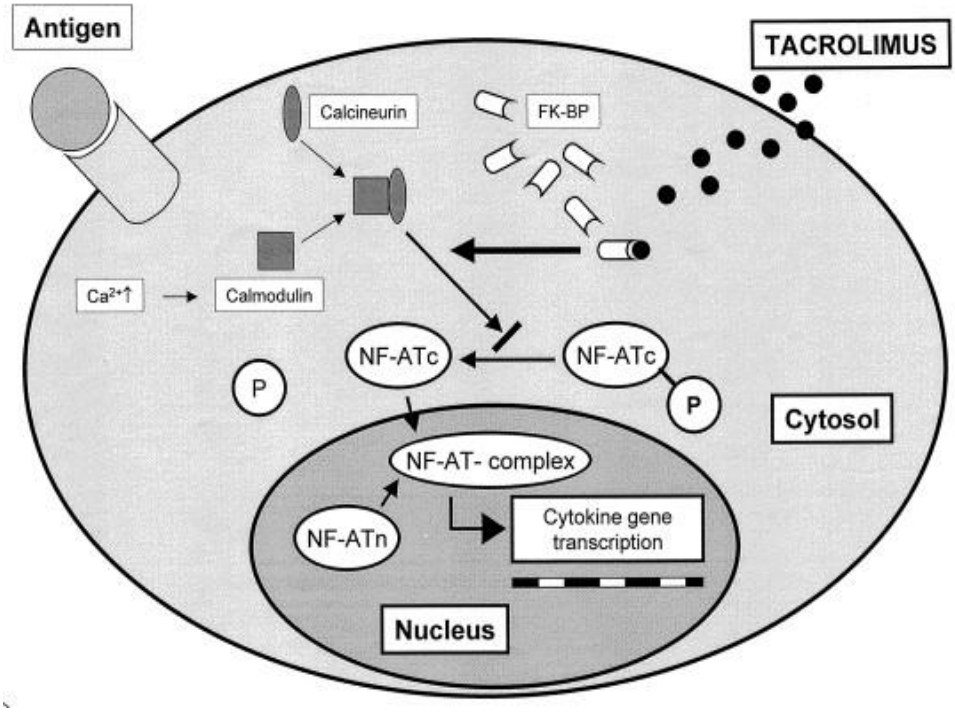


MECHANISM OF ACTION

Cellular mechanism of action of tacrolimus is similar to cyclosporine , though tacrolimus is 10 to 100 times more potent than cyclosporine at the molecular level. Tacrolimus after entering in to the cell binds to immunophilins known as FK 506 binding protein .

Immnunophilins are a family of highly conserved proteins helps in protein folding. The drug-immunophilin complex binds and inhibit the activity of enzyme calcineurin, which is a calcium/calmodulin dependent protein phosphatase .

Figure11: Mechanism of tacrolimus



As a result , the inhibition of calcineurin leads to

- Interruption of the calcium dependent signal transduction pathway in T cells.
- Interference with the translocation of cytosolic subunit NF-ATc nuclear factor activated T cells to the nucleus involved in the transcription of cytokine genes.
- Suppression of transcription of early T cell activation genes , which will affect the production of interleukin 2 , interleukin 3 , interferon gamma and tumor necrosis factor alpha.

Tacrolimus in vitiligo [63-65]

Calcineurin inhibitors can be effective in vitiligo therapy because of their ability to restore the altered cytokine network. Tacrolimus acts by inhibiting T cell activation via downregulation of transcription of genes encoding proinflammatory cytokines IL-2, IL-3, IL-4, IL-5, interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and granulocyte macrophage colony-stimulating factor (GM-CSF) in T cells.

Apart from the above mechanism, a direct effect of tacrolimus on melanocyte growth and migration during melanogenesis has been reported. Topical calcineurin inhibitors (tacrolimus ointment 0.03%–0.1% and pimecrolimus

ointment 1%) are generally given for treating localized vitiligo lesions of the face and neck and found to be more effective in combination with UV radiation delivered by high-fluency UVB devices.

Several studies have concised the advantages of calcineurin inhibitors

- Selective mode of action,
- Absence of skin atrophy
- Less Systemic absorption

Few additional studies are needed, as well as more information about possible risks of cutaneous and extracutaneous cancers should be emphasized.

Pharmacokinetics

- Bioavailabilty of oral tacrolimus 25% by giving orally.
- Oral absorption is variable and decreased by food.
- Cutaneous absorption of topical tacrolimus is<5%
- Tacrolimus demonstrate zero order / saturable process also requires blood level monitoring for dose adjustment.
- It is metabolised by CYP3A4 and 95% excreted through bile t1/2=12hours

Adverse effects

Oral

- Dose limiting toxicity is Nephrotoxicity
- Others includes neurotoxicity, alopecia, precipitation of diabetes and diarrhoea

Topical

- Erythema, burning sensation
- Skin cell melanoma has been proved only in rat models

OUTCOME ASSESSMENT

The Fundamental process that is necessary to evaluate the treatment efficacy is to know about the extent and severity of vitiligo[66] to make a appropriate treatment choices and make favourable prognosis.

A Systematic review shows that many randomised controlled trials for the intervention of vitiligo[67] used various types of outcome measures to determine the efficacy of vitiligo therapy .

Currently used methods to assess the severity and extent of depigmented lesion to evaluate vitiligo[68-73] :

- Vitiligo area scoring index
- Vitiligo European task force assessment

- Visual assessment methods like physician global assessment, visible light photography, ultraviolet light photography
- Vitiligo extent tensity index
- Spectrophotometry
- Point counting method
- Potential repigmentation index
- Reflectance confocal microscopy

VITILIGO AREA SCORING INDEX

This score was first introduced and validated by Hamzavi and coworkers[67] . It is validated quantitative scale to assess the severity , potential for repigmentation ,response of treatement.

Intitaly this score was introduced to evaluate the response rate of narrow band UV B .Then It was used to evaluate the activity of vitiligo and pattern of depigmentation in the skin.

In this score , patients body is divided in to

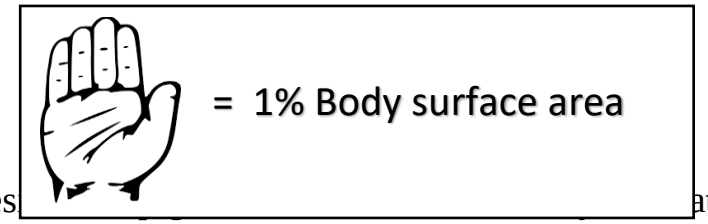
1. Hands
2. Upper extremities(includes axillary region)
3. Trunk
4. Lower extremities(inguinal region and buttocks)

5. Feet

6. Head and neck

The percentage involvement of depigmented skin in each body region is calculated by palmar method[72].

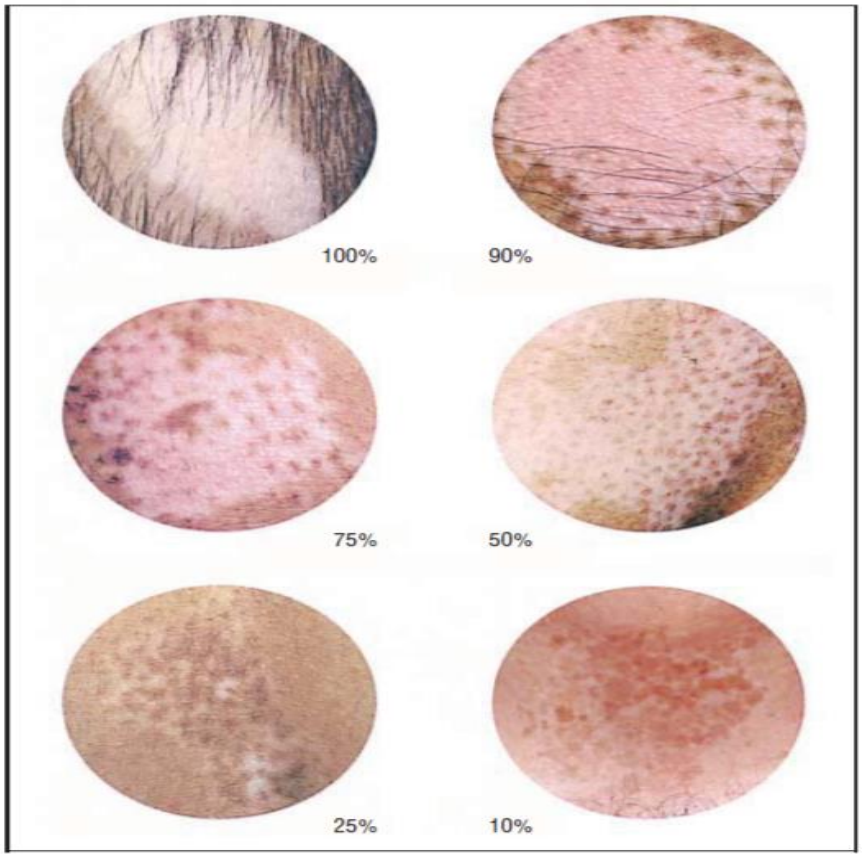
Palmar method implies that palm surface of patients hand (including volar surface of digits) of patients corresponds to 1.0% of total body surface area.



Res ating the each site by visual assessment .The pattern of depigmentation is described by following percentages 0, 10%, 25%, 50%,75%,90%,100%.

- 100%= No pigment is present.
- 90% = Specks of pigment present.
- 75% = Depigmented area exceeds the pigmented area.
- 50% = Depigmented and pigmented area.
- 25% = The pigmented area exceeds the depigmented area.
- 10% = Only specks of depigmentation are present.

Figure 12: ***Percentage Residual Depigmentation***



Then the VASI score of a patient with depigmented macules is derived by summing the values of all body sited in the form of hand units and multiplied with percentage of vitiligo involvement in affected skin.

VASI score = ∑ [HAND UNITS] × **[**RESIDUAL DEPIGMENTATION]

PERCENTAGE REPIGMENTATION[73]:

To calculate the relative repigmentation after treatment .

The formula used is

- Repigmentation rate = (1- New VASI score/Old VASI score) × 100

Grading of repigmentation in vitiligo using VASI score:

Improvement in VASI score is ranged accordingly and graded the repigmentation rate . According to the grade of repigmentation we can evaluate the efficacy of a given treatment .

Table 1: GRADING OF REPIGMENTATION

SNO	Grading of Repigmentation	% Repigmentation	Degree of Repigmentation
1.	GRADE 0	0	ABSENT
2.	GRADE I	1-25%	SLIGHT
3.	GRADE II	26% -50%	MODERATE
4.	GRADE III	51% - 75%	GOOD
5.	GRADE IV	76% -100%	EXCELLENT

AIM AND OBJECTIVE

AIM AND OBJECTIVE

AIM

To determine and compare the efficacy of topical placental extract versus topical tacrolimus when both used in combination with topical mometasone furoate in terms of repigmentation in vitiligo patients.

PRIMARY OBJECTIVES

- To Compare the efficacy of topical mometasone with topical tacrolimus versus topical mometasone with topical placental extract by evaluating the difference in mean VASI score between the two groups from baseline and at the end of 2^{nd} , 4^{th} , 8^{th} , 12^{th}, 24^{th} weeks.
- To Compare the percentage difference in Repigmentation rate between the two groups from baseline and at the end of treatment (24^{th} week).

SECONDARY OBJECTIVE

- To study the tolerability of combination therapy of topical mometasone furoate with topical tacrolimus in management of vitiligo patients
- Safety of topical tacrolimus in vitiligo patient

METHODOLOGY

MATERIALS AND METHODS

STUDY TITLE

A Comparative study of efficacy and safety of Topical mometasone furoate 0.1% with placental extract versus Topical mometasone furoate 0.1% with Topical Tacrolimus 0.1% in Vitiligo .

This study was commenced only after getting approval from the Institutional Ethics Committee of Government Stanley Medical College. The information about the research including the risk and benefits were well explained to the study participants in their own language and the written informed consent was obtained.

STUDY DESIGN

This is the Single centered , Prospective , Randomized , Open labelled, Parallel group , Comparative study. It is a non sponsored study.

STUDY CENTRE

Outpatient section of Department of Dermatology, Government Stanley medical college and Hospital, Chennai.

STUDY POPULATION

Patients diagonesd with stable vitiligo attending outpatient department of Stanley medical college.

SAMPLE SIZE

80 patients calculated based upon the samples from previous review of literature using sample size calculation formula. For Group A- 40 patients and Group B – 40 patients

STUDY PERIOD

From March 2017 to February 2017

STUDY DURATION:

24 Weeks for each patient.

Each patient received treatment for a period of 24 weeks , followed by post study observation for 4 weeks. If the VASI score of any of the study participants become zero after treatment , the drugs are stopped and the patient was followed up for 24 weeks.

SELECTION CRITERIA

Case definition

Stable vitiligo is defined as 'a patient diagnosed with vitiligo reporting no new lesions , no progression of existing lesions and there is absence of koebner phenomenon during the past 1 year'.

INCLUSION CRITERIA

- Patients between 18 to 50 years of age of either sex.
- Patients diagnosed with stable vitiligo with involvement of less than 20% body surface area.
- Patients had vitiligo with duration of disease not less than 1 year showed no spontaneous repigmentation .
- Patients with vitiligo had no treatment for the last one month.
- Patient who are willing to give written informed consent and have no objection to participate in the study.

EXCLUSION CRITERIA:

- Patients diagnosed with lip tip type of vitiligo or mucosal involvement.
- Vitiligo patients who had history of autoimmune diseases or malignant disease.
- Pregnant and lactating women, children less than 18 years of age and elderly more than 50 years of age .

- Patients with concomitant use of Vitamin D , calcium and any other drug affecting calcium metabolism.
- Patients who had known hypersensitivity to placental extract/ tacrolimus/mometasone furoate.

DRUGS USED :

1. **Topical Mometasone furoate cream 0.1%**
2. **Topical Placental extract gel**
3. **Topical Tacrolimus ointment 0.1%**

Topical Mometasone cream and Topical Placental extract gel will be supplied from the government pharmacy in the dermatological department, Stanley medical college. Topical Tacrolimus was purchased from retail outlet. The Batch number, date of manufacture, bill number from the retailer and the date of purchase will be entered in the drug treatment form for each patient.

INVESTIGATIONS

Haematological investigations

- Complete hemogram
- Platelet count
- Peripheral smear

Renal Investigations

- Urine analysis
- Albumin , sugar , deposits
- Serum uric acid
- Serum creatinine
- Blood urea

Hepatic Investigations

- Alkaline phosphatase level
- Serum proteins
- Serum transaminase

Blood sugar

Screening for HIV

ENT Examination

Dental Examination

These investigations were done prior to the selection of patients. Only those patients with normal baseline investigations were included in the study. These investigations were repeated at the end of every 4 weeks till the completion of the study.

STUDY PROCEDURE:

The patients for this study will be recruited from the outpatient Department of Dermatology, Govt Stanley Medical College, Chennai. Patients fulfilling the criteria and willing to participate in the study will be included in this study

Detailed history , clinical examination , type of vitiligo , site of involvement , size and extent of lesions were assessed. only patients with characteristic lesions consisting of clearly defined , white depigmented macules in the face, trunk and limbs were selected for the study. Lesions involving mucosa , lips and tips of fingers were excluded.

The surface area involving vitiligo was measured by palmar method , percentage involvement of depigmented area was assessed using VASI score. Photographs of the lesions were taken before commencing the study and after completing the study to compare the clinical efficacy.

Then the patients were randomized in to two groups Group A and Group B. Patients coming in even number were randomised to Group A and patients coming in the odd number were randomised to Group B.

GROUP A:

All the patients in Group A were given standard treatment which was given in the dermatology department. This group served as a standard group.

Topical Mometasone furoate cream 0.1% once daily + Topical Placental extract gel twice daily . Local application for 24 weeks.

GROUP B:

All the patients in the group B were treated with Topical Mometasone furoate cream 0.1% once daily + Topical Tacrolimus 0.1% twice daily. Local application for 24 weeks. This group serves as study group.

Application of topicals was instructed to the patient based on fingertip method.

Follow up:

Patients will be assessed twice weekly during the first month ,once monthly there after and final result was compared at the end of 24 weeks. Patients followed up to 28 weeks after completion of study period. Patients continuously monitored for improvement and adverse effects. Photographs of vitiliginous skin were taken at first visit and after 3^{rd} and 4^{th} month . At each visit, pigmentation and adverse effects noted.

The clinical improvement was evaluated by calculating the vitiligo area scoring index VASI Score at baseline , 2^{nd} , 4^{th}, 8^{th} , 12^{th} and 24^{th} week. Responses

will be graded on a vitiligo noticeability scale from 0-5 based on the repigmentation rate .

ADVERSE EVENT MONITORING

Patients were closely monitored for adverse events after application of treatment. Adverse effects were noted mainly based on self reporting by the patients.

Patients were questioned for adverse effects like burning , itching and pain at each visit.

COMPLIANCE

Compliance of the patient was confirmed by asking them to return the empty tubes on the next visit. On returning the tubes only , new tubes were given to the patient.

In this study , compliance were good in almost all the patients.

STATISTICAL ANALYSIS:

Data was compiled at the end of the study, data was compiled in the Excel spread sheet. VASI score was expressed as mean + standard deviation

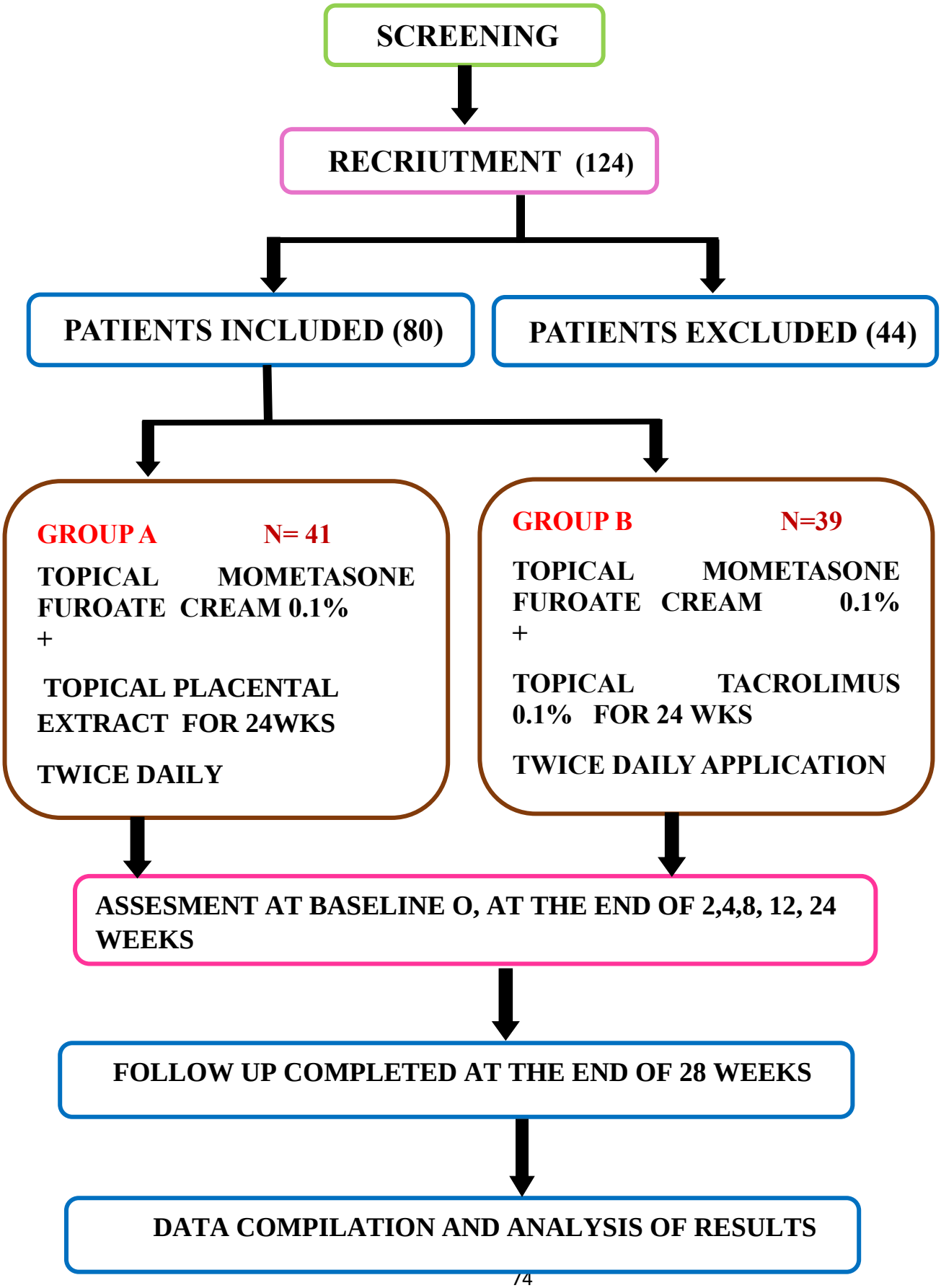
.students independent ‘t’ test was used for analysing quantitative data between the groups. Chi square was used to analyse qualitative data between the groups.

At the end of the study , the effects of topical mometsone with topical placental extract and topical mometasone with topical tacrolimus was compared in terms of therapeutic efficacy and adverse events.

SKIN BIOPSY

After obtaining written informed consent, skin biopsy was done for 3 cases in each group before starting the therapy and 14 weeks after treatment. Skin biopsy was done under local anaesthesia with aseptic precautions. The biopsy specimen was sent to the pathology lab in presence of 10 % Formalin. Section was stained using eosin and haematoxylin stain and studied under low and high power microscope and the findings were recorded. The HPE findings were compared with pre-treatment and post-treatment specimen.

Photograph showing the punch biopsy for HPE examination


SCREENING
RECRIUTMENT (124)
PATIENTS INCLUDED (80)
PATIENTS EXCLUDED (44)
GROUP A N= 41
TOPICAL MOMETASONE FUROATE CREAM 0.1%
+
TOPICAL PLACENTAL EXTRACT FOR 24WKS
TWICE DAILY
GROUP B N=39
TOPICAL MOMETASONE FUROATE CREAM 0.1%
+
TOPICAL TACROLIMUS 0.1% FOR 24 WKS
TWICE DAILY APPLICATION
ASSESMENT AT BASELINE O, AT THE END OF 2,4,8, 12, 24 WEEKS
FOLLOW UP COMPLETED AT THE END OF 28 WEEKS
DATA COMPILATION AND ANALYSIS OF RESULTS

METHOD OF APPLICATION OF OINTMENT/GEL:

The Fingertip unit is the method used to quantify the dose of the cream/ ointment which was applied over the skin. The fingertip unit was first described by Long and Finlay to describe quantities of corticosteroid cream.

1 fingertip unit= 0.5 gm of cream/ointment = 2 hand(palm surface)

One fingertip unit refers to amount of ointment/gel/cream that is squeezed out of the tube on the palmar aspect of the distal index finger from the tip to the first crease of index finger.

Patients were instructed to apply $1/4^{th}$ fingertip unit as the measure of the ointment / gel over the vitiligo lesion.

One fingertip unit

RESULTS

Table 2: Age group of the patients who participated in the study

S.no	Group	Number	Mean age	S.D	Max age	Min age
1.	Group A	41	34.67	7.34	50	19
2.	Group B	39	35.01	6.51	50	18

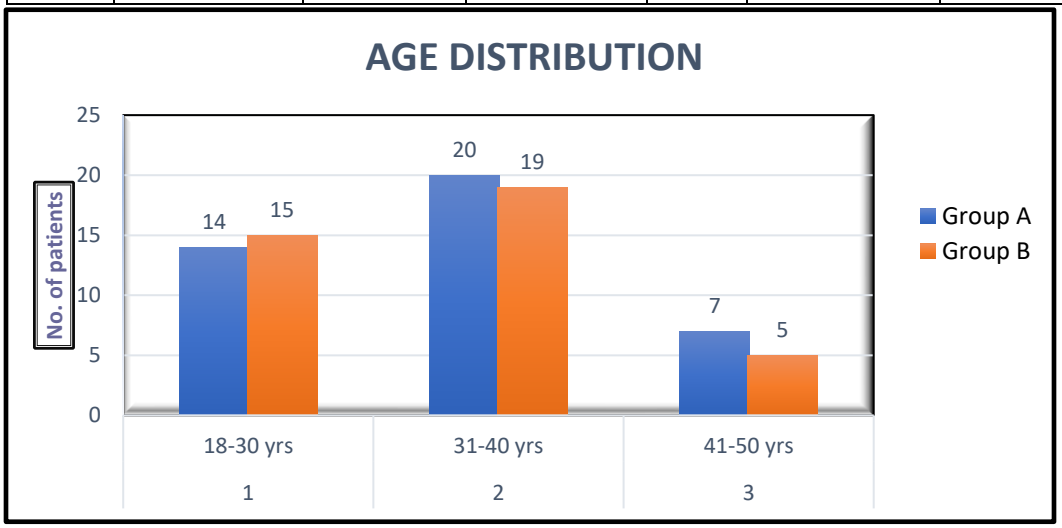


Figure 13 : ***Age distribution of the patients***

- Figure 13 illustrates the age distribution of patients in group A and group B
- In Group A, 14 patients were in the 18-30 yrs age interval vs. 15 patients in Group B
- In Group A , 20 patients were in the 31-40 yrs of age interval whereas in Group B it was 19
- In group A had 7 patients in the age interval of 41-50 yrs , whereas Group B had 5 patients .

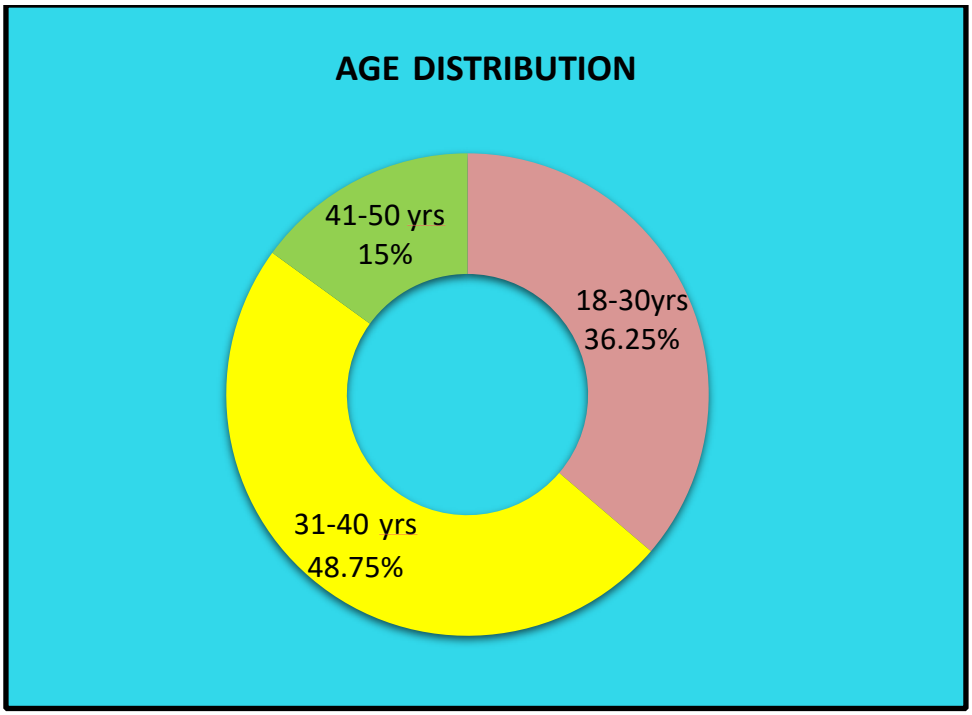


Figure 14 : ***Percentage age distribution in the study***

- Figure 14 illustrates the percentage wise age distribution of total patients in the study
- Out of 80 patients included in this study , 36.25% of patients were in the age interval 18-30 yrs .
- In our study maximum number of patients were in the age group of 31-40 yrs of age contributes about 48.75%
- Among 80 patients in the study, 15% of patients were in the age interval of 41-50yrs of age.

Table 3 :Sex distribution of patients who participated in our study

S No.	Sex	Total	Group A		Group B	
			No.	%	No.	%
1.	Male	36	20	55.55	16	44.44
2.	Female	44	21	47.72	23	52.27

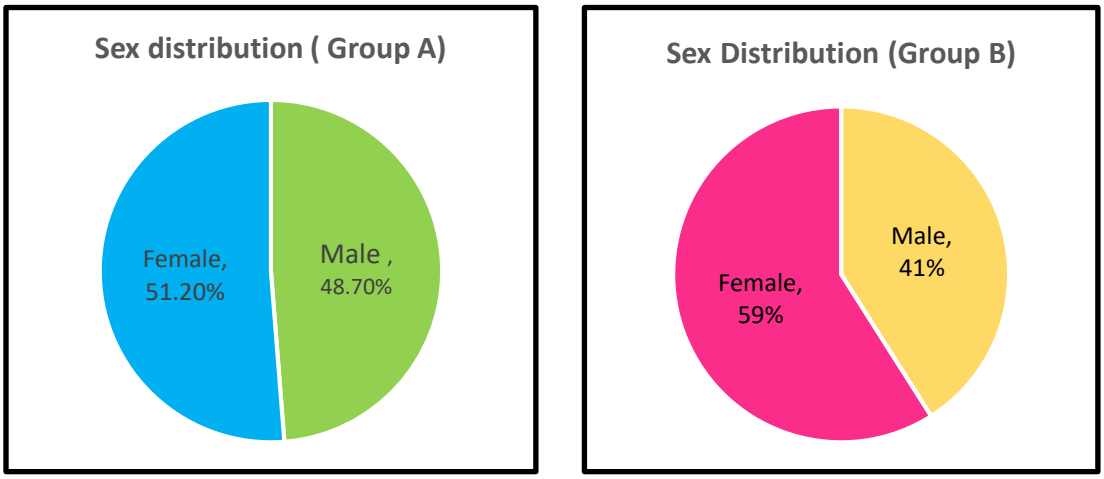


Figure 15 : *Sex distribution of patients*

Figure 15 shows the diagrammatic representation of sex distribution illustrates that

- The Gender distribution of patients in both the groups which are comparable.
- There was a female preponderance in both the groups, in which 51.20% female in Group A and 59% female in Group B when compared to males 48.70% in Group A and 41%in Group B respectively.

Table 4:VASI Score for Group A patients before and after treatment

Sno	Week 0	Week 2	Week 4	Week 8	Week 12	Week 24	Repigmentation rate
1.	16.2	16.2	13.5	13.5	9	4.5	72.2%
2.	12.75	12.75	12.75	8.5	4.25	1.7	86.6%
3.	15.3	15.3	12.75	12.75	12.75	12.75	16.66%
4.	14.25	14.25	14.25	9.5	4.75	4.75	66.66%
5.	16.2	16.2	13.5	13.5	9	9	44.4%
6.	13.5	13.5	13.5	11.25	7.5	3.75	72.22%
7.	12	12	12	12	12	12	0
8.	14.4	14.4	12	12	8	4	72.22%
9.	15.3	12.75	12.75	12.75	8.5	8.5	44.44%
10.	13.5	13.5	13.5	13.5	13.5	13.5	0
11.	17.1	14.25	14.25	14.25	9.5	4.75	72.22%
12.	13.5	13.5	13.5	11.25	7.5	3.75	72.22%
13.	16	16	14.4	12	12	8	50%
14.	12	12	12	12	12	12	0
15.	12.6	12.6	12.6	12.6	12.6	12.6	0
16.	10	10	10	10	10	10	0
17.	10.8	10.8	9	9	6	3	72%
18.	11	11	9.9	8.25	5.5	2.75	75%
19.	9	7.5	7.5	7.5	5	5	44.44%
20.	7.5	7.5	7.5	7.5	7.5	7.5	0
21.	8.1	8.1	8.1	8.1	4.5	2.25	72.22%
22.	8.1	6.75	6.75	6.75	6.75	4.5	44.44%
23.	4.5	4.5	3.75	3.75	2.5	1.25	72.22%

24.	**6.3**	**5.25**	**5.25**	**5.25**	**5.25**	**3.5**	**44.44%**
25.	**7**	**6.3**	**6.3**	**6.3**	**3.5**	**1.75**	**75%**
26.	**8.1**	**8.1**	**8.1**	**6.75**	**4.5**	**2.25**	**72.22%**
27.	**9.9**	**9.9**	**9.9**	**9.9**	**8.25**	**5.5**	**44.44%**
28.	**12**	**12**	**10.8**	**9**	**6**	**3**	**75%**
29.	**12.6**	**10.5**	**10.5**	**7**	**3.5**	**1.4**	**88.88%**
30.	**11.7**	**11.7**	**11.7**	**9.75**	**6.5**	**3.25**	**72.22%**
31.	**15**	**15**	**13.5**	**13.5**	**13.5**	**11.25**	**25%**
32.	**13.5**	**13.5**	**13.5**	**13.5**	**13.5**	**13.5**	**0**
33.	**5**	**4.5**	**3.75**	**3.75**	**2.5**	**3.75**	**25%**
34.	**6**	**6**	**5.4**	**5.4**	**5.4**	**4.5**	**0**
35.	**4.5**	**4.5**	**4.5**	**4.5**	**4.5**	**4.5**	**0**
36.	**4.5**	**4.5**	**4.5**	**3.75**	**3.75**	**2.5**	**44.44%**
37.	**6**	**6**	**6**	**5.4**	**5.4**	**4.5**	**25%**
38.	**7**	**7**	**7**	**6.3**	**6.3**	**5.25**	**25%**
39.	**8**	**8**	**8**	**7.2**	**7.2**	**4**	**50%**
40.	**6**	**6**	**6**	**5.4**	**5.4**	**3**	**50%**
41.	**4**	**4**	**4**	**3.6**	**3.6**	**3**	**25%**

Table 5: VASI SCORE for Group B before and after treatment.

	Week 0	Week 2	Week 4	Week 8	Week 12	Week 24	Repigmentation rate
1.	16.2	16.2	16.2	16.2	16.2	13.5	16.2%
2.	13.5	13.5	13.5	9	4.5	1.8	86.66%
3.	15.3	15.3	12.75	8.5	4.25	1.7	88.88%
4.	17.1	17.1	17.1	17.1	17.1	14.25	16%
5.	12.75	12.75	8.5	8.5	8.5	4.25	66.66%
6.	14.4	12	12	8	4	1.6	88.88%
7.	13.5	11.25	11.25	7.5	3.75	1.5	88.8%
8.	12	12	8	8	4	1.6	86.6%
9.	15.3	15.3	12.75	8.5	4.25	1.7	88.8%
10.	16.2	13.5	9	9	4.5	1.8	88.8%
11.	17.1	17.1	17.1	17.1	17.1	14.25	16.2%
12.	11.25	11.25	11.25	7.5	3.75	3.75	66.6%
13.	15	15	13.5	11.25	7.5	3.75	75%
14.	13.5	13.5	13.5	11.25	7.5	3.75	72.5%
15.	12.6	10.5	10.5	7	3.5	1.4	88.8%
16.	10.5	10.5	10.5	10.5	7	3.5	66.6%
17.	10.8	10.8	9	9	6	3.5	67.5
18.	11	11	9.9	8.25	5.5	2.75	75%
19.	9	7.5	7.5	7.5	7.5	5	44.4%
20.	8.25	8.25	5.5	5.5	5.5	5.5	33.33%

21.	**8.1**	**6.75**	**4.5**	**2.25**	**0.9**	**0**	**100%**
22.	**8.1**	**6.75**	**4.5**	**2.25**	**0.9**	**0.9**	**88.8%**
23.	**4.5**	**4.5**	**3.75**	**2.5**	**1.25**	**0.5**	**88.8%**
24.	**6.3**	**5.25**	**5.25**	**5.25**	**5.25**	**3.5**	**44.44%**
25.	**7**	**7**	**6.3**	**5.25**	**3.5**	**3.5**	**50%**
26.	**8.1**	**8.1**	**6.75**	**6.75**	**4.5**	**2.25**	**72.2%**
27.	**9.9**	**9.9**	**8.25**	**.25**	**5.5**	**2.75**	**72.2%**
28.	**13**	**11.7**	**11.7**	**9.75**	**9.75**	**6.5**	**50%**
29.	**11.7**	**9.75**	**6.5**	**3.25**	**3.25**	**1.3**	**88.8%**
30.	**14**	**12.6**	**10.5**	**3.5**	**3.5**	**1.4**	**90%**
31.	**15**	**13.5**	**13.5**	**11.25**	**7.5**	**3.75**	**75%**
32.	**13.5**	**11.25**	**11.25**	**3.75**	**1.5**	**0**	**100%**
33.	**5**	**4.5**	**4.5**	**3.75**	**2.5**	**1.25**	**75%**
34.	**6**	**6**	**5.4**	**4.5**	**3**	**3**	**50%**
35.	**3.75**	**3.75**	**2.5**	**1.25**	**0.5**	**0**	**100%**
36.	**6**	**6**	**5.4**	**4.5**	**0.6**	**0**	**100%**
37.	**7**	**6.3**	**3.5**	**1.75**	**0.7**	**0.7**	**90%**
38.	**6**	**5.4**	**3**	**3**	**0.6**	**0**	**100%**
39.	**4**	**3.6**	**3**	**2**	**0.4**	**0**	**100%**

REPIGMENTATION RATE IS CALCULATED AT THE END OF 24 WEEK FOR BOTH THE GROUPS.

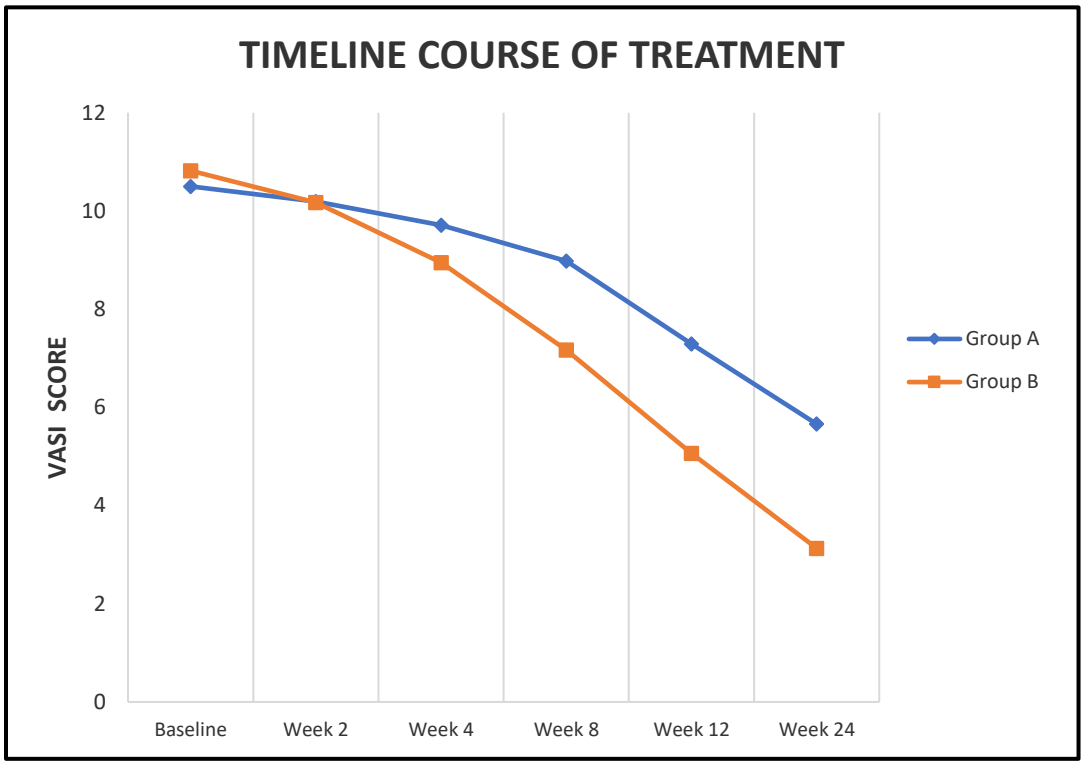
Table 6 : mean VASI score from baseline and at the end of 24 weeks for Group A and Group B

Duration	Group A		Group B		Student Independent T test
	Mean	SD	Mean	SD	
Baseline	10.50	3.91	10.82	3.97	t=0.36 , P=0.7170
Week 2	10.19	3.84	10.17	3.88	t=0.02 , P=0.9810
Week 4	9.71	3.50	8.95	4.10	t=0.89 , P=0.3745
Week 8	8.98	3.32	7.17	4.04	t=2.19 , P=0.0314*
Week 12	7.29	3.27	5.06	4.19	t=2.65 , P=0.0095***
Week 24	5.66	3.72	3.13	3.56	t=3.10 , P=0.0027***

*** P<0.05 significant , ** P<0.01 highly significant ,**

***** P<0.001 Very high significant**

Figure : 16 Assessment of VASI score between the two groups



VASI SCORING

VASI Score is vitiligo area scoring index and this scoring method is used to assess the extent , pattern and severity of vitiligo in a patient. The pattern and percentage involvement of depigmentation is calculated in both the groups using VASI score . The VASI score calculation were done before starting therapy and after treatment at the end of week 2^{nd} , 4^{th} ,8^{th} 12^{th} and 24^{th} week.

The individual VASI scores are shown in Table 4 and Table 5

On doing statistical analysis of the VASI scores, the mean value of the VASI score before starting treatment in group A is 10.50 and group B is 10.32 which is comparable.

The mean VASI score start coming down in both the groups from the end of 2^{nd} week. The reduction in mean VASI score is much greater in group B when compared to group A at the end of 2^{nd} week till completion of study (24^{th} week). At the end of 24^{th} week, mean VASI score in group A is 5.6634 and group B is 3.132

Student 't' test for VASI score shows that the P values become significant at the end of 8^{th} week (P=0.0314). Then the P values were consistently very significant at the end 12^{th} week (P=0.0095) and at the end of 24^{th} week (P=0.0027).

Figure 16 shows significant and consistent reduction of VASI score in group A when compared to group B.

Clinicaly patient shows progressive repigmentation which was calculated for both groups using percentage repigmentation rate.

Table 7:Grading of Repigmentation in group A and group B

S.NO	Grade Of Repigmentation	Mometasone (0.1%) + placental extract n=41		Mometasone (0.1%) + Tacrolimus (0.1%) n=39	
		N0.OF PATIENTS	%	N0. OF PATIENTS	%
1.	GRADE 0	8	19.51%	0	0
2.	GRADE I	7	17.07%	3	7.69%
3.	GRADE II	10	24.39%	6	15.38%
4.	GRADE III	14	34.14%	11	28.20%
5.	GRADE IV	2	4.87%	19	48.71%

Table 7 describes about the grading of repigmentation in group A and group B

Final repigmentation rate in both the groups were graded from grade 0 to grade IV

.

In group A , 8 patients didn't respond to treatment corresponds to grade 0 (19.51%). Only 2 patients (4.87%) shows excellent repigmentation rate corresponds to grade IV. None of the patients show complete repigmentation .

In group B , almost all the patients responded to treatment , none of them corresponds to grade 0 . It has been seen that 19 patients(48.71%) had excellent

repigmentaion corresponding to grade IV. Complete repigmentation of skin is recorded in 6 patients.

The clinical photographs and microscopic biopsy picture were taken before and after treatment support our findings. Statistical analysis also confirmed the above findings.

All haematological and biochemical investigations were assessed at baseline and at the end of 3rd and 4th month which did not show any significant alterations in the parameters after treatment.

Adverse effects were continuously monitored

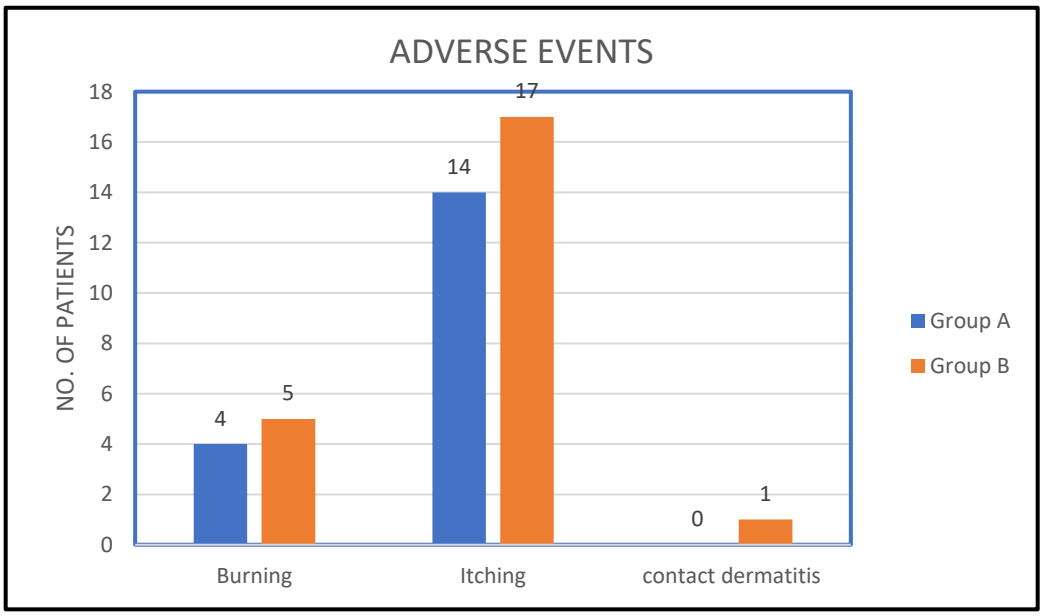


Figure 17: ***Adverse events in Group A and Group B***

Figure 17 illustrates the adverse events in both the groups

In group A , 4 patients had complaints of burning sensation but it was mild subsided within one day. It has been noted that 14 patients had complaints of itching.

In group B , burning sensation was encountered in 5 patients which is mild subsided within a day. It has been shown that 17 patients had itching in group B and 1 patient was diagnosed with contact dermatitis , treated with in a week.

There was no other serious local or systemic adverse events in both the groups . Patient compliance was good in both the groups.

DISCUSSION

DISCUSSION

In Our Open label, randomised, comparative, interventional , parallel group , we have screened 144 patients for study in dermatological OPD, 44 were excluded , 80 patients were included in our study fulfilling less than 20% of stable vitiligo . In group A there were 41 patients , 39 patients in group B. patients in group A received standard treatment of topical mometasone furoate 0.1% and placental extract gel , where as group B was treated with topical mometasone furoate 0.1% and study drug topical tacrolimus 0.1% . The repigmentation rate of study drug topical tacrolimus along with topical mometasone in 41 patients was compared with 39 patients getting standard drug treatment topical mometasone in combination with topical placental extract.

In patients with vitiligo involving less than 20% of BSA , the main stay of treatment is topical steroid therapy along with adjunctive topical therapy. But main drawback with use of topical steroid therapy is slow response rate and adverse effects like telengectasia and atrophy which is more common with very potent class 1 topical steroid. Mometasone is a class 2 potent steroid, have been found to be effective monotherapy in treatment of vitiligo in children with minimal side effects

.

Topical placental extract is an better adjunctive therapy with steroids in terms of cost effectiveness and only few studies have been conducted in vitiligo. A study conducted by Imran majid et al using topical placental extract in combination with narrowband UV B had not shown better results when compared with narrowband therapy .

Topical tacrolimus a novel drug was added to the vitiligo treatment , it also proved to be better monotherapy for treating stable vitiligo in children involving face and genitals , so here combination of steroid with placental extract was compared with steroid with tacrolimus.

Baseline demographic findings like age, sex is comparable for both groups. In our study, Age at which the onset of vitiligo is maximum at the age group of 31- 40 years of age 48.75% which was similar to the study conducted by puthiyapurayil et al .

Regarding distribution of gender , the percentage of female patients were found to be higher than male patients in both of the groups. This is almost consistent with most of the similar studies conducted . kovacs et al who already inferred in his study there is preponderance of females among the patients of vitiligo in his study.

Among the 80 patients in our study , 41 patients were in group A and 39 patients were in group B , the mean VASI score was comparable at both the group at the baseline of treatment. In group A mean VASI score at the baseline was 10.50 whereas in group B mean VASI score was 10.82(p=0.7170).

As shown in the table 6, From the end of 4th week mean VASI score started decreasing , mean VASI improvement score in group A was 9.7183 but in group B it was 8.95 (P=0.3745).

In this study , mean VASI score started decreasing by the end of 4th week itself , At the end of 8th week mean VASI improvement score in group A was 8.9866 whereas in group B was 7.1769 s showing significant difference between two groups (P=0.0314) . In the study conducted by M cavalie et al VASI improvement score started showing significant reduction at the end of 12th week only .

As shown in the table 6 , mean VASI improvement score at the end of 24th week , mean VASI score for the group B was 3.5694 which reduced to greater extent when compared to group A the mean VASI score of 5.6634(P=0.0027)

Regarding repigmentation rate , the degree of repigmentation in vitiligo was assessed by VASI score. Improvement in repigmentation rate was represented by reduction in VASI score which is then graded from Grade 0 to Grade IV.

As shown in the table 7, all the patients in group B responded to treatment atleast some repigmentation was present when compared to group A where 8 patients did not shown any repigmentation (grade 0 =19.51%).

In Group B, Excellent repigmentation (76-100%) was recorded in 19 patients (48.71%) when compared to Group A having 2 patients (4.87%) only with grade IV repigmentation as shown in table 7. Surprisingly six patients in group B showed complete repigmentation where none of them in group A showed complete recovery

.

Previous studies conducted showed that only one patient has recovered and shown complete repigmentation in topical mometasone and topical tacrolimus group.

From the results , it was clear that combination therapy of topical mometasone with topical tacrolimus were having significantly beneficial effects than standard treatment . The combination of topical momeatsone with topical tacrolimus showed marked repigmentation in the depigmented vitiligo macules.

CLINICAL IMPROVEMENT

Clinically the rate of repigmentation and reduction in VASI score was rapid in group B . This was proved statistically .

Thus the study results shows that combination therapy of topical mometasone with topical tacrolimus are producing much faster and greater beneficial results when compared to topical mometasone and topical placental extract.

ADVERSE EFFECTS

Both Group A and Group B did not produce any significant systemic adverse effects during the study except some local adverse effects like burning sensation , itching . only one patient had contact dermatitis on group B then it subsided with in a week.

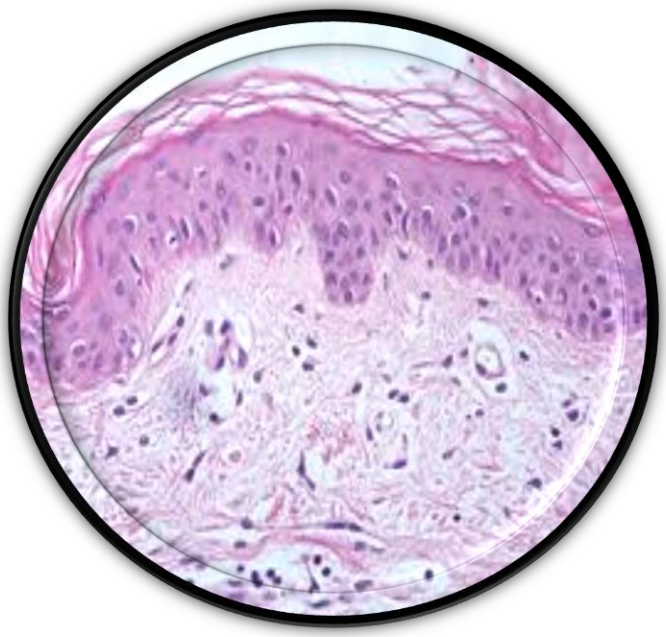
PICTURE 1:

PHOTOGRAPH SHOWING STABLE VITILIGO IN THE ABDOMEN BEFORE AND AFTER TREATEMENT IN GROUP A PATIENT.

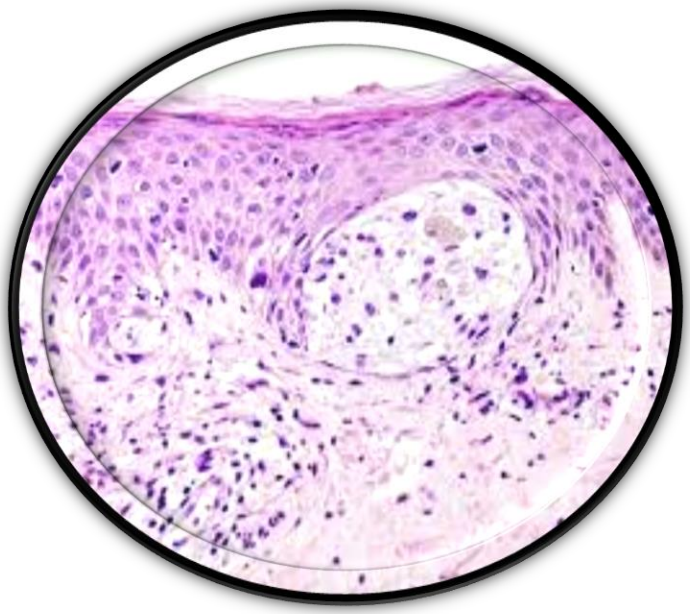
PICTURE 2 :

PHOTOGRAPH SHOWING STABLE VITILIGO IN THE LEGS BEFORE AND AFTER TREATMENT IN GROUP B PATIENT

HISTOPATHOLOGICAL PICTURE - BEFORE TREATMENT IN GROUP A

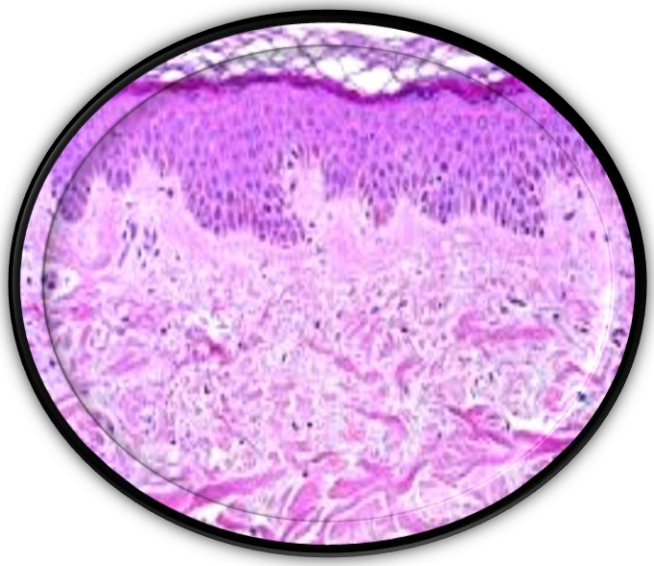


HISTOPATHOLOGICAL PICTURE - AFTER TREATMENT IN GROUP A



HISTOPATHOLOGICAL PICTURE - BEFORE TREATMENT IN GROUP B

HISTOPATHOLOGICAL PICTURE - AFTER TREATMENT IN GROUP B



HISTOPATHOLOGICAL EXAMINATION

HPE Before treatment:

Histopathological studies done before starting treatment showed there was a marked loss of melanocytes in lesional areas and some perifollicular infiltrates were present at the margins of active lesions .

HPE after completion of treatment:

HPE studies repeated after 24 weeks of therapy showed remarkable increase in the number of melanocytes in the basal areas and infiltration of lymphocytes were reduced .

HPE of skin biopsy done for both Group A and Group B before giving treatment and after completion of treatment.

CONCLUSION

CONCLUSION

In this study , topical tacrolimus 0.1% used with topical mometasone 0.1% is a better combination therapy in producing repigmentation and clinical improvement in stable vitiligo patients. Topical Tacrolimus 0.1% is a well tolerated and effective adjunctive therapy with topical mometasone for stable vitiligo.

Our study encourages usage of topical tacrolimus as a adjunctive therapy with topical momtasone furoate and can be used as a maintainence therapy to prevent relapse of depigmentation of skin . The only drawback of topical tacrolimus was the price . The cost effectiveness was not described in this study .

BIBLIOGRAPHY

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ANNEXURES

CASE PROFORMA

Name:

Age:

Sex:

Hospital No:

Complaints:

Diagnosis :

Treatment History:

General Examination:

Vital signs :

Anaemia/Lymphadenopathy:

Pedal Edema/Jaundice:

Systemic Examination:

CVS RS

ABDOMEN CNS

LOCAL EXAMINATION :

……
…….....

DIAGNOSIS:

TREATMENT:

VASI score at

Baseline, 2nd week, 4th week,8th week,12th week, 24th week

% Repigmentation rate

Baseline, 2nd week, 4th week , 8th week, 12th week, 24th week

ADVERSE EFFECTS:

Baseline, 2nd week, 4th week, 8th week , 12th week, 24th week

தகவல் படிவம்

வெண்தோல்படலம் சரும நோய்க்கான சிகிச்சையில் மொமட்டசோன் ப்யூரேட் 0.1% களிம்புடன் பளிசென்டா சர்ம களிம்பு கூட்டு மருந்து மற்றும் மொமட்டசோன் ப்யூரேட் 0.1% களிம்பு கூட்டுமருந்து செயல்திறன் மற்றும் பாதுகாப்பு பற்றிய ஒப்பீட்டு ஆய்வு, அரசு ஸ்டான்லி மருத்துவக் கல்லூரி மற்றும் மருத்துவமனையில் பொது மருத்துவத்துறையில் மரு.அ.பிரீத்தி மருந்தியல் துறை (பட்ட மேற்படிப்பு மாணவர்) அவர்களால் அனுபவம் வாய்ந்த மருத்துவர்களின் மேற்பார்வையில் நடத்தப்படுகிறது.

இந்த ஆய்வில் பயன்படுத்தப்படும் மருந்துகள் ஏற்கனவே உபயோகத்தில் உள்ள மருந்தேயாகும். புதிய மருத்துகள் எதுவும் உபயோகபடுத்தப்படவில்லை.

இந்த ஆய்வு 24 வாரங்கள் நடைபெறுகிறது. இந்த ஆய்விற்கு தேவையான தோல் பரிசோதனையும் தோல் சிகிச்சையும், ஆய்வின் துவகத்திலும், 24 வாரங்களில் ஆய்வு முடிந்தவுடனும் தோல் பரிசோதனை செய்யப்படும்.

இந்த ஆய்வில் கலந்து கொள்ள நீங்கள் தகுதியானவர் தானா என்று அறிந்து கொண்ட பின்னரே நீங்கள் சேர்த்துக் கொள்ளப்படுவீர்கள்.

இந்த ஆய்வு முடிவுகள் மருத்துவம் சம்பந்தமான வெளியீடுகளில் உங்களுடைய சுய அடையாளமின்றி வெளியிடப்படும்.

இதில் விருப்பமில்லாவிடில் இந்த ஆய்விலிருந்து நீங்கள் எப்பொழுது வேண்டுமானாலும் விலகிக் கொள்ளலாம். அவ்வாறு விலகிக் கொள்ளும் பட்சத்தில் உங்களுக்கு அளிக்கப்படும் சிகிச்சை நிறுத்தப்படாது.

சுய ஒப்புதல் படிவம்

..... என்ற விலாசத்தில் வசிக்கும் திரு/திருமதி. ..... ஆகிய நான் அரசு ஸ்டான்லி மருத்துவக்கல்லூரி மற்றும் மருத்துவமனையில் நடத்தப்படும் ஆய்வான வெண்தோல்படலம் சரும நோய்க்கான சிகிச்சையில் மொமட்டசோன் ப்யூரேட் 0.1% களிம்புடன் பளிசென்டா சர்ம களிம்பு கூட்டு மருந்து மற்றும் மொமட்டசோன் ப்யூரேட் 0.1% களிம்பு கூட்டுமருந்து செயல்திறன் மற்றும் பாதுகாப்பு பற்றிய ஒப்பீட்டு ஆய்வு நடத்தப்படுகிறதுல் என்று தெரிந்து கொண்டேன்.

இந்த ஆய்வு மருத்துவர் அ.பிரீத்தி அவர்களால் அனுபவம் நிறைந்த மருத்துவர்களின் உதவியோடு நடத்தப்படுகிறது என்று தெரிந்து கொண்டேன்.

இந்த ஆய்வு 24 வாரங்கள் நடக்கும் என்றும் இந்த ஆய்வில் மருந்தின் செயல்திறன் காண தோல் பரிசோதனை மற்றும் தோல் சிகிச்சை செய்யப்படும் என்றும் தெரிந்துக் கொண்டேன்.

இந்த ஆய்வில் கலந்த கொள்ள முழு மனதுடன் சம்மதிக்கிறேன்.

இந்த ஆய்வில் முடிவுகளை மருத்துவம் சம்பந்தமான வெளியீடுகளில் சுய அடையாளமின்றி வெளியிட சம்மதிக்கிறேன்.

எனக்கு விருப்பமில்லாவிடில் நான் இந்த ஆய்விலிருந்து எப்பொழுது வேண்டுமானாலும் விலகிக் கொள்ளலாம் எனத் தெரிந்து கொண்டேன்.

அவ்வாறு விலகி கொள்ளும் பட்சத்தில் எனக்கு அளிக்கப்படும் சிகிச்சை நிறுத்தப்படாது எனவும் தெரிந்து கொண்டேன்.

பெயர் :

நாள் :

கையொப்பம் :

இடம் : அரசு ஸ்டான்லி
மருத்துவமனை
சென்னை-1.